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# Re-evaluation of the KMSK scales, rapid dimensional measures of self-exposure to specific drugs: Gender-specific features

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ABSTRACT

*Background:* The Kreek-McHugh-Schluger-Kellogg (KMSK) scales provide a rapid assessment of maximal self-exposure to specific drugs and can be used as a dimensional instrument. This study provides a re-evaluation of the KMSK scales for cannabis, alcohol, cocaine, and heroin in a relatively large multi-ethnic cohort, and also the first systematic comparison of gender-specific profiles of drug exposure with this scale.

*Methods:* This was an observational study of n = 1,133 consecutively ascertained adult volunteers. The main instruments used were the SCID-I interview (DSM-IV criteria) and KMSK scales for cannabis, alcohol, cocaine, and heroin.

*Results:* Participants were 852 volunteers (297 female) with specific DSM-IV abuse or dependence diagnoses, and 281 volunteers without any drug diagnoses (154 female). Receiver operating characteristic (ROC) curves were calculated for concurrent validity of KMSK scores with the respective DSM-IV dependence diagnoses. The areas under the ROC curves for men and women combined were 99.5% for heroin, 97% for cocaine, 93% for alcohol, and 85% for cannabis. Newly determined optimal KMSK "cutpoint" scores were identical for men and women for cocaine and heroin dependence diagnoses, but were higher in men than in women, for cannabis and alcohol dependence diagnoses.

*Conclusions:* This study confirms the scales' effectiveness in performing rapid dimensional analyses for cannabis, alcohol, cocaine, and heroin exposure, in a cohort larger than previously reported, with "cutpoints" changed from initial determinations, based on this larger sample. The KMSK scales also detected gender differences in self-exposure to alcohol and cannabis that are associated with the respective dependence diagnoses.

## 1. Introduction

Recent trends in substance use disorder (SUD) research are giving greater emphasis to dimensional bio-behavioral measures, in addition to categorical diagnoses (Beseler and Hasin, 2010; Keyes et al., 2011; Kwako et al., 2018). Dimensional variables are those for which a measurement can be made along some form of a continuum (e.g., severity, amount of use, or another clinical measure). Such dimensional measures can be useful for the design of prevention efforts, disease characterization, and for genetic association studies (Crystal et al., 2012; Sloan et al., 2017). Maximal self-exposure to a specific drug can be a useful measure, and also has translational relevance, since it can be examined similarly in some preclinical models. Maximal self-exposure can be operationally defined as the frequency, duration and amount of use for the period in a person's life when use is the heaviest.

One dimensional measure of self-exposure to specific drugs of abuse is obtained with Kreek-McHugh-Schluger-Kellogg (KMSK) scales, which have been examined for concurrent validity with DSM-IV dependence diagnoses in relatively small groups of participants (Kellogg et al., 2003; Tang et al., 2011). In these prior determinations, the concurrent validity of KMSK scores was especially high for opioid and cocaine dependence diagnoses (e.g., AUROC of 0.99 and 0.98, respectively),

*Abbreviations:* 95%CI, 95% Confidence Interval; AUROC, Area Under the Receiver Operating Characteristic Curve; FDR, False Discovery Rate; IQR, Inter-Quartile Range; KMSK, Kreek-McHugh-Schluger-Kellogg scale for maximal self-exposure to specific drugs; ROC, Receiver Operating Characteristic Curve; SUD, Substance Use Disorders

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and slightly lower for alcohol and cannabis dependence diagnoses. The KMSK scales for specific drugs have been used to characterize self-exposure in different clinical populations, and also as a phenotypic measure for genetic association studies (Crystal et al., 2012; Jackson et al., 2010; Khoury et al., 2010; Vassileva et al., 2013). These scales provide ordinal measures of maximal self-exposure, focusing on the period in a participant's life at which use of a specific drug was the heaviest. While several other valuable and extensive instruments are available in the SUD field (Hasin et al., 2015; McLellan et al., 2006), the KMSK scales may be especially useful in providing a rapid dimensional measure of maximal self-exposure to several major drugs. The amount of drug exposure has been extensively examined as a construct in preclinical studies and shown to be critical for the emergence of addiction-like behavioral and neurobiological consequences (Ahmed and Koob, 1998; Fagergren et al., 2003; Mantsch et al., 2004; Willuhn et al., 2012).

Categorical diagnoses for SUD are typically based on the presence of several specific clinical criteria (e.g., escalation of drug use, tolerance, withdrawal, and persistent desire for the drug, as well as other criteria). Preclinical and clinical studies suggest that different neurobiological and neuroanatomical systems can mediate these different phenomena (Bencherif et al., 2004; Han et al., 2006; Valenza et al., 2016; Volkow et al., 2014). For example, preclinical studies suggest that acute rewarding effects of some drugs may be mediated more prominently by the ventral striatum (including Nucleus Accumbens), whereas the dorsal striatum (Caudate-Putamen) may be more prominently involved in habit-like drug-taking behaviors that occur after escalation and chronic self-exposure (Valenza et al., 2016; Willuhn et al., 2012). It is also known that particular brain areas, such as the locus coeruleus in the brainstem, may be more prominently involved in the development of classic opioid withdrawal signs (Han et al., 2006). It may, therefore, be of value to determine if a rapid dimensional measure of drug exposure has a stronger predictive value for specific criteria for each drug, as these may be related to different underlying neurobiological mechanisms.

In this study, we therefore carried out a re-evaluation of the KMSK scales for cannabis, alcohol, heroin, and cocaine with a multi-ethnic cohort larger than those previously reported, from a large multi-ethnic urban area. This analysis also includes the first examination of gender differences in dimensional aspects of drug-self-exposure, with this instrument. Several recent studies have shown that specific aspects of drug use can differ between genders (Carliner et al., 2017b; Hasin and Grant, 2015; Hoertel et al., 2014).

## 2. Methods

This was an analysis of a cohort composed of 1,133 sequentially ascertained volunteers (ascertained in April 4 2002-August 1 2013), examined as outpatients at a research hospital in the New York City area. These volunteers were originally recruited for genetic association studies of SUD.

### 2.1. Volunteer recruitment, inclusion, and exclusion criteria

The protocol was approved by the Rockefeller University Hospital Institutional Review Board (IRB). Recruitment of volunteers was completed with IRB-approved notices and local newspaper postings. All volunteers provided signed informed consent for the study.

#### 2.1.1. Study inclusion criteria

Inclusion criteria were being ≥18 years of age, able to comprehend study procedures, and able to comprehend and sign the informed consent in English.

#### 2.1.2. Study exclusion criteria

Volunteers unable to comprehend study procedures or informed consent, such as those with uncontrolled schizophrenia or other psychotic disorders, were excluded (Bond et al., 1998).

#### 2.1.3. Diagnostic categories of volunteers under study

A person was categorized as a healthy volunteer if they did not meet any DSM-IV drug abuse or dependence diagnoses. In addition, since ascertainment of this cohort was designed for genetic association studies of addictive diseases (Bond et al., 1998), people would not be in the healthy volunteer category if they had any of the following histories: **(i)** drinking to intoxication within the 30 days prior to ascertainment; **(ii)** any illicit drug use including opiates, cocaine, and amphetamines (but not including cannabis) during the 30 days before ascertainment; **(iii)** usage of illicit drugs (excluding cannabis) at least three times a week for a period of one month or more during their lifetime; **(iv)** if they had used cannabis during more than 12 days during the 30 days before ascertainment. These conditions, therefore, allowed for broad normative exposure to cannabis and alcohol in the volunteers without any drug diagnoses.

The statistical analyses conducted here, such as ROC analyses, correlations, and regressions, focused on the relationship of KMSK data and cannabis, alcohol, cocaine or opioid *dependence* diagnoses (non-mutually exclusive). However, data for *abuse* diagnoses were also recorded and are briefly summarized (see Supplementary Table 2).

### 2.2. Questionnaires and diagnostic categories

Volunteers were sequentially ascertained on an outpatient basis, at the Rockefeller University Hospital. Each volunteer underwent a private, face-to-face interview with a licensed clinician (e.g., M.D., D.O., Ph.D. Psychologist, Nurse Practitioner or Registered Nurse). This interview was carried with "pen and paper" versions of the two instruments below.

#### 2.2.1. Structured clinical interview for lifetime diagnosis (SCID) I/P (Version 2.0), for DSM-IV criteria (First et al., 2002)

In addition to lifetime DSM-IV dependence diagnoses for the aforementioned drugs, we also examined the presence of specific clinical criteria for the drugs. In order to focus on criteria with translational potential, we focused on phenomena that have been studied extensively in preclinical models, such as escalation of drug intake, tolerance, and dependence/withdrawal (Altarifi and Negus, 2015; Li et al., 2016; Winger and Woods, 2001; Zernig et al., 2007). The DSM-IV criteria selected for study here therefore were: **a)** "use of the drug at greater amounts than originally intended" (abbreviated to "greater amounts"), **b)** "persistent desire to use the drug" (abbreviated to "persistent desire"), **c)** "tolerance" and **d)** "withdrawal".

#### 2.2.2. KMSK scales (Kellogg et al., 2003)

The KMSK scales provide a rapid dimensional measure of maximal self-exposure specific drugs, focusing on cannabis, alcohol, heroin, and cocaine in this study (scales for other drugs are available, but not examined here). These scales can be completed in a clinical interview, typically within < 5 min per drug examined. Each scale provides an ordinal integer estimate of maximal self-exposure to a drug, focusing on the time in a participant's life when use was the heaviest. The scale for each drug ranges from "0″ (no exposure/never used) to a maximal score. The KMSK score for each drug is the composite sum of three subscores: "frequency" (times/day), "duration" (years), and "amounts used in a sitting or day". Table 1 has a summary of the KMSK scales and subscores; KMSK scales were previously characterized for their concurrent validity to respective DSM-IV drug dependence diagnoses, with males and females combined (Kellogg et al., 2003; Tang et al., 2011). Separate versions of the KMSK scale are also available for the past 30 days (these were not used herein). The full text of the lifetime and "past 30 day" KMSK scales is freely available, and also includes forms for other drugs in addition to those used here (http://lab.rockefeller.edu/kreek/assets/