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Test–re-test reliability of DSM-IV adopted criteria for 3,4-methylenedioxymethamphetamine (MDMA) abuse and dependence: a cross-national study

Linda B. Cottler, Kit Sang Leung & Arbi Ben Abdallah

Epidemiology and Prevention Research Group, Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA

ABSTRACT

Aims This study evaluated the prevalence and reliability of DSM-IV adopted criteria for 3,4-methylenedioxymethamphetamine (MDMA) abuse and dependence with a purpose to determine whether it is best conceptualized within the category of hallucinogens, amphetamines or its own category. **Design** Test–re-test study. **Participants** MDMA users (life-time use >5 times) were recruited in St Louis, Miami and Sydney ($n = 593$). The median life-time MDMA consumption was 50 pills at the baseline. **Measurements** The computerized Substance Abuse Module for Club Drug (CD-SAM) was used to assess MDMA abuse and dependence. The Discrepancy Interview Protocol (DIP) was used to determine the reasons for the discrepant responses between the two interviews. Reliability of diagnoses, individual diagnostic criteria and withdrawal symptoms was examined using the kappa coefficient (κ). **Findings** For baseline data, 15% and 59% met MDMA abuse and dependence, respectively. Substantial test–re-test reliability of the diagnoses was observed consistently across cities ($\kappa = 0.69$). 'Continued use despite knowledge of physical/psychological problems' (87%) and 'withdrawal' (68%) were the two most prevalent dependence criteria. 'Physically hazardous use' was the most prevalent abuse criterion. Six dependence criteria and all abuse criteria were reported reliably across cities (κ: 0.53–0.77). Seventeen of 19 withdrawal symptoms showed consistency in the reliability across cities. The most commonly reported reason for discrepant responses was 'interpretation of question changed'. Only a small proportion of the total discrepancies were attributed to lying or social desirability. **Conclusion** The adopted DSM-IV diagnostic classification for MDMA abuse and dependence was moderately reliable across cities. Findings on MDMA withdrawal support the argument that MDMA should be separated from other hallucinogens in DSM.

Keywords Club drugs, ecstasy, MDMA, reliability, test-re-test.

Correspondence to: Linda B. Cottler, Washington University School of Medicine, 40N Kingshighway, Suite 4, St Louis, MO 63108, USA. E-mail: cottler@epi.wustl.edu
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INTRODUCTION

3,4-methylenedioxymethamphetamine (MDMA), or ecstasy, is categorized as a controlled substance worldwide (Schedule I in the United States), with a high abuse/dependence liability [1]. After a marked decline in the rates of use from 2002 to 2003, the trend leveled off for 2 years and then increased in 2006 [2–4]. In 2006, over 12 million individuals 12 or older reported using MDMA at least once in their life-time, with 2.1 million reporting use in the past 12 months [2], indicating MDMA's continued popularity among youth.

MDMA is classified currently in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), as a hallucinogen, despite its strong stimulant properties. The typical preparation of MDMA, known as ecstasy, contains the racemic mixture of bioactive (S) and (R) MDMA enantiomers which are known to cause both stimulant and hallucinogenic effects in humans. Although MDMA is structurally similar to both mescaline-type hallucinogens and amphetamine-type stimulants, it is different pharmacologically from any other substance classes [5,6]. Given the high prevalence rate of MDMA use, the harmful consequences of its use

and the distinctive pharmacology of MDMA, we have been arguing for a separate substance class with its own set of substance specific diagnostic criteria for this substance [7–9].

Early studies on MDMA use provided some evidence for disordered use. Three studies emphasized MDMA's amphetamine-like chemical structure and applied the DSM criteria for amphetamine use disorders to determine MDMA abuse and dependence. Handо *et al.* [10] found that 64% of MDMA users ($n = 185$) met criteria for dependence and 21% met criteria for abuse, with withdrawal (98%), tolerance (83%) and unsuccessful attempts to stop (43%) common. Yen & Hsu [11] found that 22% ($n = 200$) of adolescent MDMA users from a juvenile abstinence center met adopted DSM criteria for MDMA dependence, with 24% reporting tolerance and 6.5% withdrawal. Schuster *et al.* [12] found the prevalence of MDMA dependence to be 20% among 3021 community adolescents. Other studies treated MDMA as a hallucinogen (as in DSM-IV), and found that MDMA users had a higher risk of dependence [odds ratio (OR) = 6.3] compared to lysergic acid diethylamide (LSD)-only users within 24 months after the onset [13,14].

Previous studies provided preliminary evidence for MDMA abuse and dependence, yet the diagnostic criteria applied either excluded MDMA withdrawal (as for hallucinogens) or limited the number of withdrawal symptoms to six (as for amphetamines). Previous research found a much wider range of withdrawal symptoms in addition to those six symptoms [7], which imply that the criteria utilized by those studies are too restrictive for MDMA. More importantly, two properties of the clinical utility of such a classification need testing—reliability of MDMA abuse and dependence, and cross-cultural applicability.

Cottler *et al.*'s study [7], one of the first to report not only the evidence for MDMA abuse and dependence, but also the reliability of the diagnosis, was limited by a small sample size ($n = 52$) of young club drug users in St Louis. Diagnostic criteria for MDMA dependence were based on the seven generic criteria for substance dependence listed in DSM-IV. To determine MDMA withdrawal, a list of 19 withdrawal symptoms was compiled from all other drug-specific withdrawal symptoms in DSM. In this study, 43% and 34% of the MDMA users met the DSM criteria for dependence and abuse, respectively. Specifically, more than half (59%) met criteria for withdrawal by either reporting at least three of the 19 withdrawal symptoms or endorsing withdrawal relief. Furthermore, the diagnosis for abuse/dependence consequent to MDMA use was reliable (kappa = 0.58).

The present study extends our previous investigation of disordered use of MDMA evaluating MDMA use, abuse and dependence and reliability of DSM-IV adopted criteria in three geographically diverse cities, to further the discussion that MDMA should be conceptualized within its own category. Demonstrating reliability among users from three different sites would be a first step in arguing a separate substance use disorder category for MDMA.

METHODS

Participant recruitment

Data were collected as part of the National Institute on Drug Abuse (NIDA)-funded TriCity Study of Club Drug Use, Abuse and Dependence among club drug users in St Louis, Missouri, Miami, Florida and Sydney (Australia) from 2002 to 2005. Eligible participants were those who used ecstasy more than five times in their life-time, with at least one use occurring in the past 12 months. Participants were recruited actively and systematically from the three communities through advertising flyers, internet postings, posters in universities and high schools, street and club outreach and public announcements in local newspapers [15]. Study protocols were approved by the Washington University School of Medicine Institutional Review Board (IRB), and the IRB at each of the participating institutes. Informed consent was obtained from all participants.

Instruments and procedures

The Substance Abuse Module for Club Drugs (CD-SAM)

The computerized CD-SAM assessed abuse and dependence associated with MDMA use. The CD-SAM is an expanded version of the Composite International Diagnostic Interview—Substance Abuse Module (CIDI-SAM) [16,17]. As with the original SAM, the CD-SAM is structured to elicit detailed information about substance use, onset and recency of use, withdrawal symptoms for each substance and DSM substance-specific diagnostic criteria. It also includes substance-specific items on medical, physical and psychological consequences.

An important feature of the CD-SAM is the separate assessment of each club drug, including MDMA, ketamine, gamma-hydroxybutyric acid (GHB) and flunitrazepam (Rohypnol). To determine disordered use of MDMA, the DSM-based diagnostic algorithm used by Cottler *et al.* [7] included meeting at least three of the seven dependence criteria in a 12-month period, while abuse of MDMA was defined as meeting at least one DSM-IV abuse criterion. To determine withdrawal for MDMA, a list of 19 withdrawal symptoms was compiled from all drug-specific withdrawal symptoms in DSM. A positive diagnosis of MDMA withdrawal required at least three of these or withdrawal relief. The CD-SAM also collects information about the use, abuse and dependence

on 13 other substances, including alcohol, marijuana, hallucinogens, stimulants, cocaine, sedatives, inhalants, opioids, ketamine, GHB, flunitrazepam, phencyclidine (PCP) and anabolic steroids. The threshold for assessing this history is use of the substance more than five times in a life-time.

The computerized CD-SAM was used in both the baseline (the first interview) and the re-test (the second interview). Most participants returned for the re-test exactly a week after the baseline (52%, median duration between the two interviews = 7days, range 3–14 days). No statistical difference was found between cities in the duration between the two interviews [Kruskal–Wallis test (2, $n = 593$) = 0.60, $P = 0.74$]. To minimize bias, a second independent interviewer, blind to the baseline responses, conducted the re-test. All interviewers completed a 5-day intensive training (provided by L.B.C.), then practised for another week, before being certified to administer the instrument. The interviews were tape-recorded and reviewed by the quality control manager. Participants were remunerated $15 after the baseline and $40 after the re-test for time and effort.

The Discrepancy Interview Protocol (DIP)

The DIP, developed by Cottler *et al.* [18–20], determined reasons for the differences in the answers between the baseline and the re-test. Due to the large number of questions in the CD-SAM, a set of 14 predetermined questions with presumably low reliability were selected, with 10 possible reasons for discrepancies between test and re-test. They included answers such as not understanding the question, cannot remember the answer, not paying attention and saying 'no' to shorten the interview.

The DIP is administered at the end of the re-test interview; the interviewer checks the responses to the predetermined questions for the two interviews. When a discrepant response is found, the interviewer asks for the explanation.

Analyses

The simple and weighted kappa coefficients [21,22] were used to examine the agreement between the two interviews. The homogeneity of kappas across cities (H_0: $\kappa_1 = \kappa_2 = \kappa_3 = \kappa$) was examined using the χ^2 statistic [23,24]. A common kappa was calculated to represent the overall test–re-test reliability when no statistical significance difference between cities was found [23]. Kappas of 0.61 or greater are generally considered substantial to excellent agreement; values between 0.41 and 0.60 represent moderate agreement and values smaller than 0.4 indicate poor agreement [25]. All analyses used the SAS version 9.1 program.

RESULTS

Characteristics of participants

Among the 640 participants enrolled, two who had used ecstasy fewer than six times in their life-time and 33 without a re-test were excluded. Among the remaining 605, 11 participants with a re-test outside the 2-week window and one outside the eligible age range (15–50 years) were excluded. The final sample consisted of 593 participants (93% completed), with 278 participants from St Louis (56% male), 178 from Miami (61% male) and 137 from Sydney (61% male). The median age was 22 years [mean = 23.31 (5.00), range 16–47 years]. No gender or age differences were noted between sites. Educational status varied across sites [χ^2 (2, $n = 593$) = 8.26, $P < 0.05$], with Miami having the highest percentage of participants with a high school diploma (49% versus 36%). While the majority of the participants in St Louis and Sydney were Caucasian (≅73%), 57% in Miami were Hispanic [χ^2 (6, $n = 593$) = 283.93, $P < 0.001$]. In Miami, all participants endorsed being comfortable conducting an interview in English.

The median number of life-time MDMA pills consumed was 50 {mean = 212 [standard deviation (SD) = 502]}; Sydney and Miami had significantly more pills than St Louis [Kruskal–Wallis test (2, $n = 592$) = 28.39, $P < 0.001$]. The mean onset age of MDMA was 19 years (SD = 4.10); 10% of users began MDMA use before age 16.

Almost all participants reported life-time alcohol or marijuana use (99.7% and 97.5%, respectively). The majority reported using hallucinogens (64%), stimulants (62%) or cocaine (61%); almost half reported sedatives (51%), inhalants (50%) or opioids (47%). On average, six other substances were reported (SD = 2.64). While most started using marijuana before MDMA (86%), more than two-thirds reported sedatives, flunitrazepam, cocaine, ketamine, anabolic steroids or GHB after or simultaneous with the onset of MDMA use. More than half (57%) of hallucinogen users and 41% of stimulant users reported using those substances before MDMA.

MDMA abuse and dependence

Neither abuse nor dependence, abuse only, and dependence categories were determined based on DSM-IV nomenclature [7]. Table 1 presents the percentage of participants meeting each diagnostic category and the reliability of the diagnoses between the baseline and the re-test (weighted kappas). Overall, the proportion meeting MDMA dependence/abuse only criteria at baseline and re-test was 59%/15% and 57%/18%, respectively. The proportion of the categories varied by city [χ^2 (4, $n = 593$) = 11.50, $P = 0.02$ at baseline; χ^2 (4,

Table 1 Percentage of 3,4-methylenedioxymethamphetamine (MDMA) users meeting DSM-IV criteria for abuse and dependence and the test–re-test reliability of diagnostic results.

	St Louis (n = 278)				*Miami (n = 178)*				*Sydney (n = 137)*				*Total (n = 593)*			
Diagnosis	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	*κ[b]*	*95% CI*	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	*κ[b]*	*95% CI*	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	*κ[b]*	*95% CI*	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	*Common κ[c]*	*95% CI*
Dependence (with or without abuse)	52.2/50.0	44.6			64.0/61.8	55.1			66.4/64.2	56.2			59.0/56.8	50.4		
Abuse only	16.6/19.0	10.1			14.6/18.5	11.2			10.2/13.1	4.4			14.5/17.5	9.1		
Neither abuse nor dependence	31.3/30.9	24.5			21.4/19.7	14.6			23.4/22.6	16.8			26.5/25.6	19.7		
Total		79.1	0.71	0.65–0.78		80.9	0.65	0.54–0.76		77.4	0.62	0.49–0.75		79.3	0.69	0.63–0.74

[a]Raw agreement between the two interviews. [b]Weighted kappa. [c]The common kappa was calculated where differences in kappas between cities were not statistically significant ($P > 0.05$). CI: confidence interval.

$n = 593) = 12.37$, $P = 0.02$ at re-test] (results not shown). St Louis had a lower percentage of MDMA-dependent users compared to Miami and Sydney. Test–re-test reliability of MDMA use disorder diagnosis was substantial: the weighted kappas for St Louis, Miami and Sydney were 0.71, 0.65 and 0.62, respectively; test–re-test reliability of diagnoses was consistent across cities [χ^2 (2, $n = 593) = 2.14$, $P = 0.34$], with a common kappa of 0.69 for the overall reliability between the two interviews.

Dependence criteria

Table 2 presents percentages, ordered by DSM-IV, of individual dependence criteria and reliability of these criteria. For the dependence criteria with more than one associated symptom in CD-SAM (i.e. 'withdrawal' and 'continued use despite knowledge of physical or psychological problems'), the associated symptoms were examined separately. 'Continued use of MDMA despite knowledge of physical or psychological problems from it' and 'withdrawal' were the two most frequently reported dependence criteria at the baseline (87% and 68%, respectively) and the re-test (84% and 62%, respectively); the least reported was 'persistent desire to cut down or control MDMA use' (17% at both interviews). 'Tolerance' was the most reliably reported criterion (common $\kappa = 0.77$), followed by 'withdrawal' (common $\kappa = 0.58$) and 'important activities given up to MDMA use' (common $\kappa = 0.57$). The least reliable was 'persistent desire to cut down' (common $\kappa = 0.53$). More than 60% of users reported at least three withdrawal symptoms from MDMA (common $\kappa = 0.57$); 11% reported withdrawal relief (common $\kappa = 0.59$).

Abuse criteria

As shown in Table 3, reports of 'failure to fulfill role obligations' and 'use despite knowledge of social problems' varied across cities. Overall, the most frequently reported abuse criterion was 'physically hazardous use', followed by 'use despite knowledge of social problems', 'failure to fulfill role obligations' and 'legal problems'. Criteria were moderately reliable (common κ ranged from 0.59 to 0.73). Five associated symptoms of 'use despite knowledge of social problems' were examined separately. The overall prevalence ranged from 2% ('physical fights') to 28% ('continued use despite knowledge of problems'), with a test–re-test reliability (common κ) ranging from 0.47 ('problems with friends') to 0.72 ('problems with family'), indicating consistency in the test–re-test reliability across cities.

Withdrawal symptoms

Table 4 shows the rates of individual withdrawal symptoms and the corresponding reliability. Symptoms were

Table 2 Percentage of 3,4-methylenedioxymethamphetamine (MDMA) users meeting individual DSM-IV criteria for substance dependence and the test–re-test reliability of individual dependence criteria.

	St Louis (n = 278)				*Miami (n = 178)*				*Sydney (n = 137)*				*Total (n = 593)*			
Dependence criteria (associated symptoms)	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	κ	*95% CI*	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	κ	*95% CI*	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	κ	*95% CI*	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	*Common* κ[b]	95% CI
Tolerance[c]	43.7/43.3	90.3	0.80	0.73–0.87	55.6/51.7	82.6	0.65	0.54–0.76	56.2/54.0	90.5	0.81	0.71–0.91	50.2/48.3	88.0	0.77	0.72–0.82
Withdrawal[c,d,e]	64.4/56.1	78.1	0.55	0.45–0.64	67.4/65.7	80.3	0.56	0.43–0.69	76.6/70.1	87.6	0.68	0.55–0.82	68.1/62.2	80.9	0.58	0.52–0.65
(Withdrawal symptoms $\geq$ 3)	63.7/55.0	77.7	0.54	0.44–0.64	64.6/65.2	79.2	0.54	0.42–0.67	75.9/70.1	86.9	0.67	0.53–0.81	66.8/61.6	80.3	0.57	0.50–0.64
(Withdrawal relief)	11.2/9.4	92.5	0.59	0.43–0.75	14.6/11.2	91.0	0.60	0.43–0.78	13.9/13.9	89.8	0.57	0.37–0.77	12.8/11.0	91.4	0.59	0.49–0.69
Using more MDMA than intended[c]	37.8/35.3	77.3	0.51	0.41–0.62	47.8/41.0	78.7	0.57	0.45–0.69	48.2/46.7	81.0	0.62	0.49–0.75	43.2/39.6	78.6	0.56	0.49–0.63
Persistent desire to cut down or control MDMA use	14.8/15.1	84.5	0.39	0.24–0.54	18.0/15.7	87.6	0.56	0.40–0.73	21.9/20.4	88.3	0.65	0.49–0.81	17.4/16.5	86.3	0.53	0.44–0.62
Too much time involved in getting or using MDMA[c,e,f]	48.6/42.8	86.3	0.73	0.64–0.81	61.8/52.8	76.4	0.52	0.40–0.66	62.8/55.5	82.5	0.64	0.51–0.77	55.8/48.7	82.5	–	–
Important activities given up to MDMA use[c,e]	20.5/14.8	87.1	0.56	0.43–0.68	24.2/16.9	88.2	0.64	0.50–0.78	34.3/24.8	78.8	0.50	0.34–0.65	24.8/17.7	85.5	0.57	0.49–0.65
Continued use of MDMA despite knowledge of physical or psychological problems from it[g]	83.8/82.4	86.3	0.51	0.38–0.65	89.3/88.2	93.3	0.66	0.49–0.84	89.1/81.0	86.1	0.46	0.26–0.66	86.7/83.8	88.4	0.54	0.45–0.64
(Used despite knowledge of physical problems)	75.9/75.2	82.0	0.51	0.40–0.63	80.9/79.8	83.2	0.47	0.30–0.63	78.9/75.9	88.3	0.67	0.52–0.82	78.1/76.7	83.8	0.55	0.47–0.63
(Used despite knowledge of psychological problems[h])	74.8/68.7	80.9	0.53	0.42–0.64	83.2/78.1	91.6	0.73	0.60–0.86	77.4/66.4	78.8	0.48	0.33–0.64	77.9/71.0	83.6	–	–

[a]Raw agreement between baseline and re-test. [b]Common kappas were calculated where differences in kappas between cities were not statistically significant ($P > 0.05$). [c]Denoted a statistically significant variation in the prevalence across cities at the baseline (χ^2test: $P < 0.05$). [d]Withdrawal criterion was met if three or more than three withdrawal symptoms were reported (withdrawal symptoms $\geq$ 3) or when withdrawal relief was reported. [e]Denoted a statistically significant variation in the prevalence across cities at the re-test (χ^2test: $P < 0.05$). [f]Differences in kappa between cities reached statistically significant level (likelihood χ^2, 2df = 7.40, $P = 0.025$), the common kappa was not calculated. [g]Criterion of continued use of MDMA despite knowledge of physical of psychological problems was met if either continued use despite knowledge of physical problems or continued use despite of psychological problems were reported. [h]Differences in kappa between cities reached statistically significant level (likelihood χ^2, 2df = 7.60, $P = 0.022$); the common kappa was not calculated. CI: confidence interval.

Table 3 Percentage of 3,4-methylenedioxymethamphetamine (MDMA) users meeting individual DSM-IV criteria for substance abuse and the test–re-test reliability of individual abuse criteria.

	St Louis (n = 278)				*Miami (n = 178)*				*Sydney (n = 137)*				*Total (n = 593)*			
Abuse criteria (associated symptoms)	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	*κ*	*95% CI*	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	*κ*	*95% CI*	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	*κ*	*95% CI*	*% of users meeting the criterion at baseline/re-test*	*Raw[a] agreement (%)*	*Common κ[b]*	*95% CI*
Failure to fulfill role obligations[c,d]	19.8/18.7	88.9	0.64	0.53–0.76	23.0/14.0	84.3	0.49	0.33–0.65	37.3/31.4	81.0	0.58	0.44–0.72	24.8/0.2	85.7	0.59	0.51–0.66
Physically hazardous use	50.0/54.0	86.0	0.72	0.64–0.80	51.1/52.3	87.6	0.75	0.66–0.85	51.8/51.1	84.7	0.69	0.57–0.81	50.8/52.8	96.2	0.72	0.67–0.78
Legal problems	3.6/3.6	98.6	0.79	0.59–0.99	6.7/3.9	96.1	0.61	0.35–0.87	4.4/4.4	100.0	1.00	–	4.7/3.9	98.2	0.73	0.57–0.88
Use despite knowledge of it causing social problems[d,e]	23.7/20.1	87.8	0.64	0.53–0.75	28.1/20.2	82.0	0.51	0.37–0.66	32.1/30.7	82.5	0.59	0.45–0.74	27.0/22.6	84.8	0.60	0.52–0.67
(Problems with family)	15.8/14.4	92.1	0.69	0.57–0.81	23.6/15.2	89.3	0.66	0.53–0.80	30.7/23.4	91.2	0.78	0.66–0.90	21.6/16.7	91.1	0.72	0.64–0.79
(Problems with friends)	15.1/11.9	88.9	0.52	0.38–0.67	18.5/8.4	85.4	0.39	0.21–0.57	17.5/11.7	86.9	0.50	0.27–0.68	16.7/10.8	87.4	0.47	0.37–0.57
(Problems at work/school)	8.6/6.1	93.9	0.55	0.37–0.74	11.2/6.2	91.6	0.47	0.25–0.70	16.8/16.8	89.8	0.63	0.46–0.81	11.3/8.6	92.2	0.57	0.46–0.68
(Physical fights)	2.9/2.9	97.8	0.61	0.33–0.90	1.7/3.9	97.8	0.59	0.23–0.95	1.5/0.7	99.3	0.66	0.04–1.00	2.2/2.7	98.2	0.61	0.40–0.82
(Continued use despite knowledge of problems)	25.2/21.9	88.1	0.67	0.57–0.77	29.8/21.4	82.6	0.55	0.41–0.69	32.9/31.4	82.5	0.60	0.46–0.74	28.3/24.0	85.2	0.62	0.55–0.69

[a]Raw agreement between baseline and re-test. [b]Common kappas were calculated where differences in kappas between cities were not statistically significant ($P > 0.05$). [c]Denoted a statistically significant variation in the prevalence across cities at the baseline (χ^2test: $P < 0.05$). [d]Denoted a statistically significant variation in the prevalence across cities at the re-test (χ^2test: $P < 0.05$). 'Criterion for 'use despite knowledge of it causing social problems' was met if a participant reported any of the associated symptoms (problems with family/problems with friends/problems at work or at school/physical) together with 'continued use despite knowledge of the problems'. CI: confidence interval.

ordered by the baseline prevalence (in descending order). The five most commonly reported symptoms (at both interviews) were 'feel depressed', 'feel tired or weak', 'change in appetite', 'have trouble concentrating' and 'feel anxious, restless or irritable'. The kappas for those ranged from 0.44 to 0.66, in the moderate to substantial range. The least reported were running eyes or nose and seizures. Among the 19 withdrawal symptoms, eight showed statistically significant variations in prevalence across cities. Two symptoms ('tremble or twitch' and 'have vivid, unpleasant dreams') also varied across cities in one of the interviews, with Sydney having higher prevalence rates of 'seeing, hearing or feeling things that were not there', trouble concentrating and trouble sleeping; Sydney also had a lower rate of MDMA craving compared to St Louis and Miami (Z-tests, $P < 0.05$, results not shown). Seventeen of 19 symptoms showed consistency in the reliability across cities.

Sources of discrepancy

Table 5 shows discrepant answers from baseline to re-test, the percentages in favor of the responses given at the baseline and the re-test, and reasons for discrepant answers. The three items with the highest number of discrepancies were 'feeling anxious, restless or irritable', trouble concentrating and 'using more MDMA than intended'. Despite this, these three items were still reported reliably both within and across cities. The item with the lowest number of discrepancies was 'withdrawal relief', one of the associated symptoms of 'withdrawal'. Participants were asked to determine which response was correct (baseline or re-test). Of the 10 predetermined reasons for discrepancy, the most commonly reported reasons were 'interpretation of question changed' (39%), 'did not understand the question' (13%) and 'do not know' (12%). Fortunately, the least reported reasons were 'the interviewer was wrong and miscoded or misunderstand the response' (0.3%) and 'participant was too embarrassed or thought that the interviewer would disapprove' (0.6%). Only eight of the 446 withdrawal-related discrepancies (1.8%) were due to a participant's misinterpreting a withdrawal symptom of MDMA that was also attributed to other substances used with MDMA. Additionally, the DIP was used to determine whether participants frequently gave their second answer as the correct answer. Findings of the 'resolved response' showed that, of the 13 DIP items, only three items were resolved in favor of the baseline and only two were resolved in favor of the re-test, suggesting that there was no systematic bias in favor of either interviews.

Table 4 Percentage of 3,4-methylenedioxymethamphetamine (MDMA) users reporting MDMA-specific withdrawal symptoms and the test–re-test reliability of individual withdrawal symptoms.

	St Louis (n = 278)				*Miami (n = 178)*				*Sydney (n = 137)*				*Total (n = 593)*			
Withdrawal symptoms	*% of users reported the symptom at baseline/re-test*	*Raw[a] agreement (%)*	*κ*	*95% CI*	*% of users reported the symptom at baseline/re-test*	*Raw[a] agreement (%)*	*κ*	*95% CI*	*% of users reported the symptom at baseline/re-test*	*Raw[a] agreement (%)*	*κ*	*95% CI*	*% of users reported the symptom at baseline/re-test*	*Raw[a] agreement (%)*	*Common κ[b]*	*95% CI*
1 Feel depressed	52.2/44.6	85.3	0.71	0.62–0.79	57.3/51.1	81.5	0.63	0.51–0.74	62.8/53.3	80.3	0.60	0.47–0.73	56.2/48.6	83.0	0.66	0.60–0.72
2 Feel tired, sleepy or weak	52.2/45.0	72.7	0.46	0.35–0.56	51.1/48.3	71.4	0.43	0.29–0.56	62.0/49.6	71.5	0.43	0.29–0.58	54.1/47.1	72.0	0.44	0.37–0.51
3 Have a change in appetite[c,d]	42.8/33.8	75.9	0.49	0.39–0.60	51.7/52.3	74.7	0.49	0.37–0.62	70.1/68.6	82.5	0.59	0.44–0.74	51.8/47.4	77.1	0.52	0.45–0.59
4 Have trouble concentrating[c,d]	37.4/29.9	76.6	0.48	0.37–0.59	37.6/32.0	76.4	0.48	0.35–0.62	63.5/57.7	79.6	0.57	0.43–0.71	43.5/36.9	77.2	0.51	0.43–0.58
5 Feel anxious, restless or irritable[c,d]	38.5/35.6	73.4	0.43	0.32–0.54	39.9/36.5	79.8	0.57	0.45–0.70	54.7/53.3	79.6	0.59	0.45–0.72	42.7/40.0	76.7	0.52	0.45–0.59
6 Have trouble sleeping[c,d]	30.6/27.0	78.4	0.47	0.36–0.59	32.6/36.0	73.0	0.40	0.26–0.54	49.6/43.1	74.5	0.49	0.34–0.63	35.6/33.4	75.9	0.46	0.38–0.53
7 Have a headache	32.0/28.8	79.5	0.52	0.41–0.63	33.2/29.2	79.2	0.52	0.38–0.65	32.9/27.7	80.3	0.53	0.38–0.69	32.6/28.7	79.6	0.52	0.45–0.60
8 Craving for ecstasy[c,d]	27.8/22.0	88.5	0.69	0.59–0.79	29.8/21.9	80.9	0.51	0.36–0.65	13.1/11.0	89.1	0.48	0.26–0.71	25.0/19.4	86.3	0.62	0.54–0.69
9 Have muscle pains	23.7/21.2	87.4	0.64	0.53–0.75	21.4/20.2	84.3	0.52	0.37–0.68	24.1/24.8	86.1	0.62	0.47–0.78	23.1/21.8	86.2	0.61	0.53–0.68
10 Yawn a lot	22.3/16.2	83.8	0.48	0.35–0.61	20.8/19.1	83.7	0.49	0.33–0.65	21.9/21.2	81.8	0.46	0.28–0.64	21.8/18.2	83.3	0.48	0.39–0.57
11 Have a fast heartbeat[c,d]	18.7/12.2	87.8	0.54	0.40–0.67	16.3/12.9	84.3	0.37	0.18–0.56	28.5/24.8	81.8	0.53	0.37–0.69	20.2/15.4	85.3	0.50	0.41–0.59
12 Feel nauseated to vomit	15.8/12.6	88.9	0.54	0.40–0.69	21.9/17.4	83.2	0.47	0.31–0.63	15.3/14.6	89.1	0.57	0.38–0.76	17.5/14.5	87.2	0.52	0.43–0.62
13 See, hear or feel things that were not there[c,d]	12.6/8.3	89.2	0.43	0.26–0.59	14.0/11.2	90.5	0.57	0.39–0.75	27.7/20.4	85.4	0.60	0.45–0.76	16.5/12.0	88.7	0.54	0.44–0.63
14 Sweat or have fever[c,d]	11.9/11.2	91.4	0.58	0.42–0.73	16.9/20.2	85.4	0.52	0.36–0.68	24.1/21.9	83.2	0.53	0.36–0.70	16.2/16.4	87.7	0.54	0.45–0.63
15 Have vivid, unpleasant dreams[d]	14.0/10.4	87.8	0.43	0.27–0.59	15.2/16.9	83.7	0.39	0.21–0.57	21.9/19.7	86.1	0.58	0.41–0.75	16.2/14.5	86.2	0.47	0.37–0.57
16 Tremble or twitch[c]	11.5/10.1	92.1	0.59	0.43–0.74	11.8/12.9	86.5	0.38	0.18–0.58	21.9/16.8	83.2	0.46	0.28–0.65	14.0/12.5	88.4	0.50	0.39–0.60
17 Have diarrhea or a stomach ache	10.8/9.4	92.1	0.56	0.40–0.73	16.9/14.0	83.7	0.38	0.19–0.56	13.1/14.6	91.2	0.63	0.44–0.82	13.2/12.0	89.4	0.53	0.42–0.63
18 Have runny eyes or nose[e]	6.1/3.2	95.7	0.52	0.28–0.75	6.2/3.9	91.0	0.07	−0.14–0.27	4.4/7.3	94.2	0.47	0.16–0.78	5.7/4.4	93.9	–	–
19 Have seizures[f]	0.4/0.4	99.3	–	–	1.1/0.6	99.4	–	–	0/0	100.0	–	–	0.5/0.3	99.5	–	–

[a]Raw agreement between baseline and re-test. [b]Common kappas were calculated where differences in kappas between cities were not statistically significant ($P > 0.05$). [c]Denoted a statistically significant variation in the prevalence across cities at the baseline (χ^2test: $P < 0.05$). [d]Denoted a statistically significant variation in the prevalence across cities at the re-test (χ^2test: $P < 0.05$). [e]Differences in kappa between cities reached statistically significant level (likelihood χ^2, 2 df = 9.45, $P = 0.009$); the common kappa was not calculated. [f]Kappas were not calculated due to low base rates for positive cases (less than 1%). CI: confidence interval.

Table 5 Frequencies of discrepancies, the proportions of reasons attributed to discrepant responses and the results of resolved response.

Question no.	*Symptoms*	*Total no. of discrepant answers with reasons given in DIP*[a]	*Reasons for discrepancy*											*Resolved response*	
			A %	*B* %	*C* %	*D* %	*E* %	*F* %	*G* %	*H* %	*I* %	*J* %	*K* %	*% in favor of baseline response*	*% in favor of re-test response*
D604AA	Have there been times when you used MDMA in a situation when you could have got yourself or others hurt?	82	7	15	1	0	6	0	0	2	52	6	10	45	55
D904AA	Have you often used more MDMA or used MDMA over a longer period of time than you intended?	122	16	12	2	0	7	2	1	6	44	8	2	53	47
D1004AA	Have you wanted to quit or cut down on MDMA or tried to quit or cut down but were unable to for at least a month?	75	25	12	4	1	12	1	0	1	28	9	5	44	56
D1104AA	Have you ever spent a lot of time using, planning to get, or recovering from the effects of MDMA?	97	16	7	5	0	11	1	0	3	37	13	5	63[b]	37[b]
D1204AB	Did you ever find you had to use much more MDMA to get the effect you wanted or the same amount of MDMA had much less effect than before?	68	12	12	1	1	10	3	0	7	35	10	7	54	46
D1304AA	Did you ever give up or reduce any important activities to get or use MDMA?	82	11	18	2	0	7	5	0	0	39	9	9	66[b]	34[b]
D1404AA01	During the first few hours or days of not using MDMA, did you ever feel depressed?	99	10	8	6	0	6	2	0	11	41	13	2	45	55
D1404AA02	During the first few hours or days of not using MDMA, did you ever feel anxious, restless or irritable?	136	11	13	5	1	13	1	0	5	36	14	1	36[b]	64[b]
D1404AA03	During the first few hours or days of not using MDMA, did you ever have trouble concentrating?	131	9	9	6	0	18	2	1	3	38	12	1	45	55
D1404AA19	During the first few hours or days of not using MDMA, did you ever crave MDMA?	80	9	6	8	0	13	1	1	8	31	21	3	43	57
D1504AA	Have you ever used MDMA to avoid or get rid of those so-called withdrawal symptoms caused by MDMA?	51	22	10	2	0	8	0	2	0	39	10	8	48	52
D1604AB	Did you continue to use MDMA after you realized it was causing any of these physical health problems?	84	21	10	4	0	4	2	2	0	44	12	1	39[b]	61[b]
D1704AB	Did you continue to use MDMA after you realized it was causing any of these emotional or psychological problems?	91	10	8	2	0	10	2	1	1	44	13	9	61[b]	39[b]
Totals		1198													
Proportion of total of 1198(%)			13.3	10.8	4.0	0.3	10.0	1.8	0.6	3.9	39.4	11.8	4.3		

Reasons for discrepancy were: A—Respondent (R) did not understand the question; B—R could not remember the answer at that time; C—R's situation has changed since the first interview; D—the interviewer was wrong and miscoded or misunderstood the response; E—R was not paying attention on one occasion; F—R said 'no' to shorten the interview/lied; G—R was too embarrassed/thought interviewer would disapprove; H—R did not really know what the right answer was; I—R's interpretation of question changed; J—do not know; K—other. [a]Number of participants completing the Discrepancy Interview Protocol (DIP) = 590. Not all participants answered all questions. [b]Differences in proportion reached the statistical significant level (Z-statistics, $P < 0.05$). MDMA: 3,4-methylenedioxymethamphetamine.

DISCUSSION

The aim of this study was to examine the prevalence and reliability of adopted DSM-IV diagnostic criteria for MDMA in different communities, and to determine whether MDMA should be considered a separate substance category. Life-time MDMA abuse or dependence was found among more than 70% of users, with more than half meeting criteria for MDMA dependence—comparable with our previous studies in the United States [7,26] and an Australian study [10].

One of the hallmarks of a classification system is its reliability and cross-cultural applicability. Validity of the clinical diagnosis is constrained by its reliability [27–31] and the diagnostic classifications have little practical value if the diagnostic results cannot be reproduced consistently. In the present study, although the proportion of MDMA abuse and dependence varied across cities, the diagnostic results were obtained reliably both within and across cities. Our findings demonstrate not only substantial reliability for the diagnostic results in each study site, but also consistency of reliability across sites, suggesting the applicability of the diagnostic classifications in different communities. The present findings are important, given the absence of cross-national research on the reliability of diagnostic classifications for MDMA use disorder in the field.

Perhaps the finding most relevant to our argument for separating MDMA from other hallucinogens is that more than 68% (baseline) of users reported enough symptoms to meet a 'withdrawal' syndrome, a syndrome not yet recognized in DSM-IV. In the present study, 'withdrawal' was the second most frequently reported criterion for MDMA dependence, with consistent test–re-test reliability across different cities. Subsequent analyses on the two associated symptoms for 'withdrawal' showed that, at the baseline, 67% of the MDMA users reported at least three of the 19 withdrawal symptoms and 13% had ever used MDMA to avoid or rid themselves of any of those withdrawal symptoms ('withdrawal relief'). These findings agree with the DSM-IV diagnostic features of substance withdrawal which highlight a substance-specific maladaptive behavioral change (with physiological and cognitive concomitants) due to the cessation of, or reduction in, substance use. Users did experience MDMA withdrawal and were able to report these specific experiences reliably. Indeed, the structural and pharmacological distinctiveness of MDMA, the evidence for disordered use of the substance and the reliable self-report of MDMA specific withdrawal together provide strong support for separating MDMA from other hallucinogens in a diagnostic classification system such as DSM.

It is less clear whether MDMA should also be separated from the amphetamine class when individual withdrawal symptoms are considered. Although MDMA users reported a wide range of withdrawal symptoms associated with the cessation of, or reduction in, MDMA use, four of the six most commonly reported symptoms overlap with those for amphetamines, including 'feel depressed', 'have a change in appetite', 'feel anxious, restless or irritable' and 'have trouble sleeping'. While this may suggest that both substances share some commonalities, it is not possible to say whether MDMA should be grouped as amphetamine at this stage because many non-amphetamine-specific withdrawal symptoms were also reported reliably by users. An important question regarding the self-reported withdrawal symptoms is whether these symptoms can be corroborated by findings in controlled settings of humans. To date, most research on the physiological dependence on MDMA focuses on tolerance, acute and subacute effects and long-term neurological damage [32–34]; withdrawal symptoms for MDMA have rarely been examined in controlled settings. A recent animal study showed that acute administration of 5-$HT_{1/2}$-serontonergic antagonist (metergoline) and $\beta_{1/2}$-adrenergic antagonist (timolol) induced a withdrawal syndrome in mice treated chronically with MDMA, while both D_1- and D_2-dopaminergic antagonists (SCH23390 and raclopride) failed to produce relevant behavioral manifestations of withdrawal, such as paw tremor and face rubbing, suggesting the possibility of a MDMA-specific withdrawal syndrome not attributable to its amphetamine-like properties [35]. However, due to the lack of controlled studies on MDMA withdrawal, the biological mechanisms underlying these non-amphetamine-specific withdrawal symptoms remain unclear.

Related to this issue is polysubstance use. Consistent with other MDMA studies, polysubstance use was prevalent here [7,10–12]. One way to test the hypothesis that MDMA users can differentiate consequences from their use of MDMA and other substances would be to evaluate users with both MDMA histories and other drug histories. They would then be compared on symptom reports to both substances to understand how they can differentiate the behaviors. If no differences were found between consequences for MDMA and other substances among users of both, it could be said that users are not able to separate the effects. This type of analysis was carried out on a sample of cocaine users; they were found to be able to differentiate different classes of substances [36].

Other dependence criteria reported most frequently by the participants include 'continued use of MDMA despite knowledge of physical or psychological problems', 'too much time involved in getting or using MDMA' and 'tolerance'. The prevalence of 'continued use of MDMA despite knowledge of physical or psychological problems' was high (87%), and should be re-evaluated for all the substances. While most users were aware of the deleteri-

ous consequences associated with MDMA use, the possession of this knowledge did not deter use of the substance. This discrepancy between 'doing' and 'knowing' poses a serious challenge to the educational programs aimed to increase the awareness of the harmful consequences associated with MDMA use. It is hypothesized that actual drug use behaviors are influenced more by the perception of risks associated with the substance rather than the awareness of risks *per se* [37].

The test–re-test reliability of individual dependence criteria was generally lower than that of the final diagnostic results. This is not unexpected, as a high item-by-item reliability is more difficult to achieve compared to that of a composite score [38]. Because the composite diagnosis for dependence was determined only by the total number of criteria reported, the final diagnoses obtained in the two interviews could be the same even when two different groups of individual criteria were reported in the two interviews. Despite the inherent difficulties in obtaining a high item-by-item reliability, moderate to substantial test–re-test reliability was observed in all individual dependence criteria and reliability was consistent across cities.

Consistent with previous studies [7,10,26], 'physically hazardous use' was the most frequently reported abuse criterion (51%). All four abuse criteria were reported reliably in each city and the reliability was consistent across study sites. Interestingly, as with the case of 'continued use despite knowledge of physical or psychological problems', the discrepancy between knowledge of harmful consequences and actual drug use behaviors was also observed in the context of social problems. Among those who reported knowledge of problems with family, friends, at work/school or physical fights, most continued to use MDMA despite the fact that they were aware of the problems. Although abuse is considered to be a less severe substance use problem than dependence [2,39,40], the findings that many users engaged in dangerous activities under the influence of MDMA and continued to use the substance despite the knowledge of problems is a concern.

An important feature of this study is the DIP, mixed with a test–re-test study. The DIP identifies the sources of discrepancies between the two interviews. Withdrawal symptoms and 'using more MDMA than intended' had the highest number of discrepant responses. More than a third of users with discrepant responses on these items attributed the discrepancies to a change in the way they interpreted the questions. Interpretation change constituted 39% of the reason for discrepant responses. More importantly, contrary to the common belief that a self-report of substance use behaviors is subject to desire to deceive and social desirability [41–43], in the present study only 1.8% of the discrepancies were attributed to lying or 'saying no to shorten the interview' and 0.6% were attributed to social desirability ('too embarrassed or thought interviewer would disapprove').

To conclude, these results not only highlight the existence of MDMA abuse and dependence, they also demonstrate the reliability of the diagnostic results based on DSM-IV nomenclature [7]. Consistent test–re-test reliability of the diagnostic results has been found across different communities despite the variation of MDMA abuse and dependence across study sites, suggesting a cross-national applicability of our diagnostic algorithm. The high prevalence of MDMA withdrawal among users underscores the need to evaluate this. First, in DSM-IV, MDMA is classified as a hallucinogen where 'withdrawal' is ignored. However, the exclusion of this phenomenon for MDMA may increase the false negative rate of diagnosis. Some MDMA users who have developed dependence on MDMA may be misdiagnosed as 'no disorder' or abuse and thus may not receive proper interventions. Secondly, the current DSM classification for MDMA may elicit false impressions about the addictiveness of the substance by ignoring the existence of MDMA withdrawal. Thus, it is advised that the DSM-V Workgroup considers separating MDMA from other hallucinogens in the future versions of the DSM.

Declarations of interest

None.

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