

# Temporal progression of cocaine dependence symptoms in the US National Comorbidity Survey

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## ABSTRACT

**Objective** Cocaine dependence first appeared as a diagnostic category in 1987 with the publication of DSM-III-R. While the temporal sequencing of alcohol symptoms has a long history, little such attention has been focused on cocaine dependence. This paper examines the retrospective recall of DSM-III-R cocaine dependence symptom progression among a large sample of cocaine users and the relationship of these symptoms to psychiatric comorbidity.

**Methods** Using data from the US National Comorbidity Survey, DSM-III-R criterion 'A' cocaine dependence symptoms were sequenced temporally based on age of symptom onset. Each of these numerical symptom strings was examined to determine its prevalence and association to comorbid psychiatric disorders.

**Results** Cocaine users represented 16% of the sample. Although hundreds of symptom sequence permutations are possible, only a few are highly prevalent. Subjects whose early onset symptoms are neuroadaptive (e.g. tolerance and withdrawal) are more likely to develop cocaine dependence than subjects whose early symptoms are characterized by psychosocial consequences. Furthermore, certain temporal patterns were found to increase or decrease the presence or absence of cocaine dependence and psychiatric comorbidity. Finally, psychiatric comorbidity preceded rather than followed cocaine use onset disproportionately.

**Conclusions** Like alcohol users, cocaine users follow a limited array of symptom sequence pathways from first use to dependence. By better understanding and examining the temporal progression of drug use symptoms, clinicians might improve screening and assessment activities and determine more effectively the extent of risks associated with continued pre-morbid drug use and enhance treatment-matching. We encourage clinicians to develop evaluation instruments that specifically ask patients to sequence their cocaine use-related symptoms temporally.

**KEYWORDS** Cocaine-related disorders, comorbidity, diagnosis, substance abuse detection.

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## INTRODUCTION

Although the existence of 'cocainomania' was acknowledged by the early 20th century (Musto 1973), cocaine abuse first appeared as a diagnostic category with the publication of DSM-III (American Psychiatric Association 1980); cocaine dependence emerged with

the publication of DSM-III-R in 1987 (American Psychiatric Association 1987; Cottler *et al.* 1993). These developments reflected and stimulated an improved understanding of cocaine dependence symptomatology that is still in its early development. For example, physiological tolerance, long recognized as a symptom in other drug dependence disorders, has only more recently

become recognized as a symptom of cocaine dependence (Adams *et al.* 1991).

As the desire for an empirically validated nosology of psychiatric disorders emerged (e.g. Robins & Guze 1970; Feigner *et al.* 1972; Kendell 1990; Kendler 1990), investigators sought to define a research-based construct of substance dependence. Kendell (1989) proposed that a clinical syndrome is comprised of two essential elements: a cluster of related symptoms and a distinctive temporal progression. In the case of the alcohol dependence syndrome, both elements have received considerable scholarly attention (e.g. Jellinek 1946; Park & Whitehead 1973; Orford & Hawker 1974; Chick & Duffy 1979; Cloninger 1987; Langenbucher & Chung 1995; Muthen 1995; Nelson *et al.* 1996; Watson *et al.* 1997). Investigators studying the cocaine dependence syndrome, however, have focused almost exclusively on the clustering of symptoms rather than their sequence (e.g. Khantzian 1985; Gawin & Ellinwood 1989; Craig & Olson 1992; Spealman 1992; Weiss, Griffin & Hufford 1992; Pilotte 1997; Tidey *et al.* 1998).

#### Sequencing alcohol dependence symptoms: the evidence from alcoholism

The method of temporally sequencing individual symptoms associated with alcohol dependence has had a long history (Jellinek 1952; Chick & Duffy 1979; Langenbucher & Chung 1995; Vaillant 1995; Nelson *et al.* 1996, 1998). Jellinek (1946, 1952) described four ordered phases of alcohol dependence among his sample of Alcoholics Anonymous members: the pre-alcoholic phase, the prodromal phase, the crucial phase and the chronic phase. The onset of the prodromal phase is marked by the onset of blackouts, while the crucial phase begins with the loss of control. Jellinek suggested originally that the loss of control differentiated alcohol users who were dependent from those who were non-dependent. Later research, however, found the opposite to be true. For example, among their sample of 38 men, Chick & Duffy (1979) observed that the behavioral loss of control generally preceded amnesia symptoms. More recently, using the same dataset and similar DSM-III-R criteria as this study, Nelson *et al.* (1996) found that the typical sequence of alcohol dependence symptoms is as follows: abuse (Musto 1973), impaired self-control (American Psychiatric Association 1980), the emergence of tolerance (Cottler *et al.* 1993) and finally physiological dependence (American Psychiatric Association 1987).

#### Comorbidity and cocaine dependence

Whether comorbid psychiatric conditions precipitate or follow drug use and abuse has been debated for many

years. For example, Vaillant (1995) suggested that alcoholism was a primary disorder responsible for precipitating a variety of personality and other psychiatric disorders often observed among excessive drinkers. Similarly, Zinberg (1974, 1975, 1984) suggested that the psychodynamic and personality attributes of people with substance use disorders were the consequence of their addiction rather than the cause.

Alternatively, Jacobs *et al.* (1989), Khantzian (1975, 1985, 1997), Rado (1933) and Weider & Kaplan (1969) represent a long line of theorists who propose that psychoactive substance use and gambling represent adaptations to pre-existing personal vulnerabilities. This theoretical position has become known popularly as the self-medication hypothesis (Khantzian 1975, 1985, 1997). This notion suggests that addictive behavior can serve as an anodyne for pre-existing emotional distress. For example, Rado (1933) first suggested that heroin use was a response to a 'tense depression' and Jacobs *et al.* (1989) proposed similarly that pathological gambling was an adaptation to underlying emotional distress. Previous analyses of the US National Comorbidity Survey provided evidence to support the position that alcohol use more frequently follows than it creates psychiatric circumstances (e.g. Kessler *et al.* 1994; Nelson, Heath & Kessler 1998).

In addition to the possible connection between cocaine use and psychiatric comorbidity, it is also important to examine the association between the presence of particular types of psychiatric comorbidity and sequences of cocaine symptoms. Patterns of cocaine symptoms might be connected more to some psychiatric disorders and not to others. Nelson *et al.* (1996) found that subjects whose earliest-onset symptoms of alcohol dependence are characterized by abuse are less likely than others to have comorbid disorders. Conversely, subjects whose first symptoms are withdrawal are more likely to have comorbid disorders.

As a central nervous system depressant, the nature and extent of alcohol's effects on psychiatric comorbidity might be different from the influence of stimulants such as cocaine. As a stimulant (i.e. an energizing drug), cocaine has the capacity to serve as an anodyne for dysthymia and depression (Khantzian 1975, 1985). By examining the temporal relationship between cocaine use and comorbid psychiatric conditions, we can provide evidence to illuminate the nature of this relationship.

#### Hypotheses

This study examines the role of various symptom sequence patterns in determining the clinical and diagnostic characteristics of a large sample of cocaine users. We will test the null hypothesis that the distribution of

individual symptoms and multiple symptom sequence patterns are equally prevalent. In addition, we hypothesize that there are symptom patterns that increase the likelihood that respondents will meet the diagnostic criteria for cocaine dependence and seek treatment. These patterns will be juxtaposed with symptom patterns that decrease the likelihood of satisfying the diagnostic criteria for cocaine dependence. Finally, we hypothesize that comorbid psychiatric disorders will have similar characteristics to the symptom patterns associated with cocaine use by serving both to increase and decrease the likelihood of developing cocaine dependence.

## METHODS

### Procedures

#### *Instrument and respondents*

Data for the present study derive from the US National Comorbidity Survey (NCS), a national survey conducted in the 48 contiguous states between 1990 and 1992 (Kessler *et al.* 1994). Interviewers from the Survey Research Center at the University of Michigan administered a modified version of the composite international diagnostic interview (CIDI) (World Health Organization 1990), an instrument based on the diagnostic categories of DSM-III-R (American Psychiatric Association 1987). The University of Michigan's version of the CIDI (UM-CIDI) is distinguished by its placement of diagnostic stem questions, the use of a commitment statement and other features informed by experimental survey research (Kessler *et al.* 1998). Regarding cocaine use, respondents provided retrospective data about the onset of cocaine use and any symptoms associated with such use.

Previous versions of the CIDI (i.e. CIDI-core, version 1.0) have shown favorable psychometric properties including high concurrent validity for substance use disorders, with a  $\kappa$  of 0.83 measured against ICD-10 criteria (Janca *et al.* 1992). Of particular relevance to the present study is the relative stability of the CIDI's time-related symptom items, with a test-retest concordance of 72.7% (ICC = 0.86) for age on abuse/dependence onset and 86.0% agreement for recency items (Wittchen *et al.* 1989).

The UM-CIDI instrument was administered to a sample consisting of 8098 subjects between the ages of 15 and 54. This sample represented an overall response rate of 82.4%. The multi-stage, stratified sampling strategy, survey methodology and weighting scheme have been described in detail elsewhere (Kessler *et al.* 1994; Little *et al.* 1997) and will be described more specifically later in the section focusing on data analysis. The comprehensiveness of the CIDI's drug and alcohol use sec-

tions has established the NCS database as an important resource to researchers investigating issues relating to substance abuse and dependence disorders (Anthony *et al.* 1994; Kessler *et al.* 1994; 1996, Kessler *et al.* 1997; Warner *et al.* 1995; Nelson *et al.* 1998).

### Independent variables and dependent measures

Since the NCS dataset available to the public does not include variables that represent the individual DSM-III-R symptoms for cocaine abuse and dependence, we created these variables using the original NCS algorithms (Zhao *et al.* 1994). To facilitate analysis in SPSS (SPSS Inc. 1999), we translated these algorithms from SAS programming code (SAS Institute 1988) into SPSS syntax.

To satisfy the diagnostic criteria for substance dependence, DSM-III-R requires (1) the presence of at least three of nine symptoms (criterion 'A'), and (2) that some of these symptoms must have lasted for at least 1 month or have occurred consistently over a long duration (criterion 'B') (American Psychiatric Association 1987). Table 1 summarizes the DSM-III-R diagnostic criteria and readers will find this table useful as a guide to the notation used throughout this paper.

The NCS diagnostic algorithm is similar to that of DSM-III-R. However, there are two important exceptions. First, although DSM-III-R does not indicate explicitly the number of symptoms that must satisfy duration requirements for diagnosis (i.e. criterion B), NCS requires two or more. Consequently, since the only difference between criterion A and criterion B symptoms is the duration/frequency requirement, only criterion A symptoms were sequenced in this study. Secondly, although the UM-CIDI measures the prevalence of DSM-III-R symptom 9 (i.e. use of the substance to relieve or avoid withdrawal symptoms), the instrument does not include items pertaining to the age of onset, recency or other time-related information for this particular symptom. Without these data, we were unable to sequence symptom 9 accurately. Therefore, we excluded it from all subsequent temporal analyses.

For every case, each of the remaining eight criterion A symptoms was sequenced temporally based upon age at symptom onset. This procedure yielded numerical strings described by the following subscript notation. The first subscript indicator represents the (f)irst symptom to occur, the second subscript position indicates the (s)econd symptom to occur, and so on through the (t)hird, and (l)ast symptom to occur that we examined. For example, the notation  $Sx_{fstl}$  refers to the temporal sequence of the first four occurring symptoms;  $Sx_{7654}$  defines a string of symptoms in which symptom 7 (i.e. marked tolerance as described in Table 1) occurred first,

**Table 1** DSM-III-R symptoms of substance dependence (American Psychiatric Association 1987).

Criterion A: Three out of nine symptoms required for diagnosis

- 1 Substance often taken in larger amounts or over a longer period than the person intended
- 2 Persistent desire or one or more unsuccessful efforts to cut down or control substance use
- 3 A great deal of time spent in activities necessary to get the substance (e.g. chain smoking), or recovering from its effects
- 4 Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, home (e.g. does not go to work because hung over; goes to school or work 'high', intoxicated while taken care of his or her children), or when substance use is physically hazardous (e.g. drives when intoxicated)
- 5 Important social, occupational or recreational activities given up or reduced because of substance use
- 6 Continued substance use despite knowledge of having a persistent or recurrent social, psychological or physical problem that is caused or exacerbated by the use of the substance (e.g. keeps using heroin despite family arguments about it, cocaine-induced depression, or having an ulcer made worse by drinking)
- 7 Marked tolerance: need for markedly increased amounts of the substance (i.e. at least a 50% increase) in order to achieve intoxication or desire effect, or markedly diminished effect with continued use of the same amount
- 8 Characteristic withdrawal symptoms
- 9 Substance often taken to relieve or avoid withdrawal symptoms

Criterion B

- 1 Some of the criterion A symptoms\* have persisted for at least 1 month or have occurred repeatedly over a longer period of time

\*The NCS diagnostic algorithm fixes the number of symptoms required to satisfy criterion B at two.

**Table 2** Compendium of  $S_f$ ,  $S_{x_f}$ ,  $S_{x_{st}}$ , and  $S_{x_{stl}}$  sequences and (percentage of respondents) for dependent and non-dependent cocaine users.

$S_f$ (non-dependents)	6 (38.4%), 4 (32.6%), 1 (8.4%), 8 (7.3%), 7 (7.0%), 2 (3.3%), 3 (2.3%), 5 (0.7%)
$S_f$ (dependents)	6 (31.1%), 7 (27.3%), 8 (18.9%), 4 (12.9%), 2 (3.4%), 5 (2.6%), 1 (2.1%), 3 (1.6%)
$S_{x_s}$ (non-dependents)	64 (30.3%), 41 (17.1%), 67 (5.9%), 47 (5.6%), 61 (5.5%), 86 (4.5%), 72 (4.0%)
$S_{x_s}$ (dependents)	76 (16.2%), 64 (14.7%), 87 (9.6%), 46 (4.9%), 86 (4.7%), 74 (4.4%), 62 (3.4%), 63 (3.4%), 65 (3.3%), 84 (3.2%), 28 (2.9%), 42 (2.8%)
$S_{x_{st}}$ (dependents)	765 (9.3%), 876 (7.4%), 642 (6.7%), 641 (4.2%), 654 (3.2%), 743 (3.0%), 621 (2.5%), 847 (2.5%), 286 (2.3%), 764 (2.0%), 762 (1.9%), 416 (1.9%), 487 (1.9%), 721 (1.8%), 631 (1.8%), 763 (1.8%), 753 (1.8%), 632 (1.6%), 532 (1.5%), 643 (1.5%), 465 (1.5%), 432 (1.5%), 865 (1.4%), 617 (1.3%), 463 (1.3%), 461 (1.2%), 682 (1.1%), 814 (1.1%), 714 (1.0%), 648 (1.0%), 627 (0.9%), 875 (0.9%)
$S_{x_{stl}}$ (dependents)	7654 (9.2%), 6421 (5.2%), 8765 (3.9%), 6218 (3.2%), 6417 (3.2%), 8476 (3.2%), 2865 (3.0%), 7632 (2.3%), 7621 (2.3%), 8761 (2.3%), 7651 (2.2%), 5321 (2.0%), 4652 (1.9%), 7432 (1.9%), 4321 (1.9%), 6321 (1.8%), 6543 (1.8%), 6317 (1.8%), 4167 (1.8%), 6172 (1.6%), 8654 (1.6%), 8764 (1.4%), 6821 (1.4%), 6487 (1.3%), 4876 (1.3%), 6275 (1.2%), 6428 (1.2%), 8732 (1.1%), 4873 (1.1%), 4632 (1.1%), 6541 (1.0%), 1764 (0.9%), 7821 (0.9%), 6425 (0.9%), 6435 (0.9%), 4617 (0.8%)

symptom 6 was the second symptom to occur, symptom 5 occurred third and symptom 4 was the last of the first four symptoms to occur. This progression was the most commonly reported pattern of four-symptom sequences among cocaine users who reported four or more symptoms. Table 2 summarizes the prevalence of these patterns of symptom onset. In addition, we examined both the first occurring symptom ( $S_f$ ) and the second occurring symptom ( $S_{x_s}$ ) independently of other symptoms. All other sequences involved multiple symptoms,  $S_{x_s}$ ,  $S_{x_{st}}$ , and  $S_{x_{stl}}$ .

### Data analysis

Data management was conducted with SPSS v. 10.0.5 (SPSS Inc. 1999). To account for variance estimation

issues arising from the NCS sampling design (Kalton 1983), all statistical analyses were performed using the jackknife method (Kish 1974) available in the SUDAAN v. 7.5.4 software package (Shah *et al.* 1997; Research Triangle Institute 2000). The importance of applying SUDAAN to the type of analyses performed in the present study is well documented (Brogan *et al.* 1998). Although the NCS study was designed to yield an equal probability sample of households, the probability of participation varied (Little *et al.* 1997). In addition, to be eligible for participation in this study respondents must have experienced psychiatric symptoms of some type. Consequently, to assure proper representation, we employed the appropriate weighting variable (i.e. P1FWT) that represented a '... combination of the various weights described in NCS papers to adjust for differential household size and

**Table 3** Demographic characteristics of cocaine users, grouped by total life-time symptoms.

	Total Sx = 0	Total Sx = 1	Total Sx = 2	Total Sx > = 3	NCS sample
Total N	884	96	98	230	8098
Percentage of total sample <i>n</i> = 8098	10.9	1.2	1.2	2.8	100
Percentage of all cocaine users <i>n</i> = 1308	67.6	7.3	7.5	17.6	–
Sex (%)					
Male	57.3	74.1	54.2	65.3	49.5
Female	42.7	25.9	45.8	34.7	50.5
Age (years)					
15–24	13.7	25.0	13.2	22.6	24.7
25–34	50.1	50.4	64.5	45.3	30.1
35–44	30.7	22.6	20.8	27.0	27.2
45–54	5.5	2.0	1.5	5.1	18.0
Race					
White	83.1	82.6	78.7	77.0	75.3
Black	8.6	8.3	5.5	5.2	11.5
Hispanic	6.2	6.1	4.3	14.8	9.7
Other	2.1	3.0	1.5	3.0	3.5
Marital status					
Married/cohabitating	68.5	67.6	52.5	62.6	62.9
Separated/divorced/widowed	12.7	11.4	5.5	10.4	10.0
Never married	18.8	21.0	42.0	27.0	27.1
Years of education					
0–11	11.2	15.2	13.5	29.8	22.3
12	38.1	46.9	50.3	37.2	37.4
13–15	26.5	18.3	20.1	20.4	21.7
≥16	24.2	19.6	16.1	12.6	18.6

differential non-response and poststratification' (Kessler 2000). Interested readers are encouraged to review an important NCS paper (Little *et al.* 1997) describing the study's various weighting strategies.

In addition to identifying the prevalence of symptom sequence patterns stratified by the presence or absence of life-time cocaine dependence status, we performed  $\chi^2$  and odds ratio analyses to test for relationships between the independent and dependent variables. Finally, since the purpose of this study is to examine the progression of symptoms that lead to cocaine dependence, we limited the calculation of odds ratios to the set and sequences of subclinical symptoms (i.e.  $Sx_f$ ,  $Sx_s$ , and  $Sx_{fs}$ ).

## RESULTS

### Respondent characteristics

Compared to non-users, cocaine users were more often younger, better-educated white males who were currently or previously married. Table 3 summarizes the distributions of demographic variables across cocaine use

symptom patterns; all of these variables were related significantly to the symptom patterns (all  $\chi^2$  tests,  $p < 0.01$ ). However, among the respondents who are the target sample for our analyses—that is, cocaine users with life-time symptoms—the mean number of total symptoms was not different across the categorical variables of sex ( $t = 0.44$ , NS), race ( $F = 0.50$ , NS) or marital status ( $F = 1.57$ , NS). Similarly, there was no relationship between age and number of symptoms ( $r = -0.01$ , NS). However, years of education did correlate significantly negative with number of symptoms ( $r = -0.15$ ,  $p < 0.01$ ). Nevertheless, this correlation explains only 2% of the variance associated with the number of symptoms and, although statistically significant, is not a clinically significant finding. Since the demographic factors yielded little or no meaningful influence on the number of symptoms, the remaining analyses need not adjust for these factors.

Of the 1308 subjects who had ever used cocaine, 67.58% reported no life-time symptoms. For those subjects with life-time symptoms,  $\chi^2$  analysis allowed us to reject the null hypothesis that the distribution of symptom sequence patterns and permutations of  $Sx_f$ ,  $Sx_s$ ,  $Sx_{fs}$ ,  $Sx_{fst}$  and  $Sx_{fstl}$  are equally prevalent across all cells

First symptom	Second symptom	Crude OR	95% confidence interval	Significance (p)
Related to becoming dependent				
7	Any	4.98	(1.86, 13.30)	<0.001
7	6	19.78	(3.17, 123.46) <sup>ab</sup>	<0.001 <sup>ab</sup>
8	Any	3.00	(1.14, 7.90)	<0.05
8	7	16.70	(3.51, 79.51) <sup>ac</sup>	<0.01 <sup>ac</sup>
Related to not becoming dependent				
1	Any	0.24	(0.10, 0.59)	<0.01
Any	1	0.22	(0.08, 0.59)	<0.01
4	Any	0.31	(0.15, 0.61)	<0.01
4	1	0.14	(0.03, 0.58)	<0.05

<sup>a</sup>At least one cell in the 2 × 2 table created for the analysis of this symptom pattern contained less than five subjects. The statistical significance of these associations was corroborated with a two-tailed Fisher's exact test.

<sup>b</sup>p < 0.001 (two-tailed Fisher's exact test).

<sup>c</sup>p < 0.01 (two-tailed Fisher's exact test).

( $\chi^2 = 302$ ,  $df = 7$ ,  $p < 0.001$ ;  $\chi^2 = 130$ ,  $df = 7$ ,  $p < 0.001$ ;  $\chi^2 = 567$ ,  $df = 37$ ,  $p < 0.001$ ;  $\chi^2 = 311$ ,  $df = 71$ ,  $p < 0.001$ ;  $\chi^2 = 190$ ,  $df = 70$ ,  $p < 0.001$ , respectively). For example, if all symptoms occurred randomly first, 12.5% of the users with symptoms would have reported that symptom 6 occurred first. However, the prevalence of this symptom (i.e. continued use despite adverse consequences) reported in this sample was 34%. Other first symptoms that occurred more than expected by the assumption of equal prevalence across symptoms were symptoms 4 (21%) and 7 (18%), respectively; symptom 4 is frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations and symptom 7 is the development of marked tolerance.

#### Prevalence of cocaine dependence and non-dependence

The overall prevalence of life-time cocaine dependence in the whole sample is 2.8% ( $n = 230$ ), representing 17.58% of life-time cocaine users ( $n = 1308$ ). The 2.8% rate differs slightly from the prevalence estimate (2.7%) reported previously by Anthony *et al.* (1995); this disparity appears due to changes in statistical algorithms and statistical software. Cocaine users with no life-time history of dependence represent 13.31% ( $n = 1078$ ) of the whole sample and 82.42% of all life-time cocaine users ( $n = 1308$ ).

#### Differences between non-dependent and dependent cocaine users

When the sample was stratified by life-time dependence status to permit comparison between non-dependent and dependent respondents who reported symptoms associated with cocaine use, we observed significant differences

**Table 4** Odds ratios of developing life-time dependence.

in the distribution of  $Sx_i$  ( $\chi^2 = 31.90$ ,  $df = 7$ ,  $p < 0.001$ ),  $Sx_s$  ( $\chi^2 = 44.835$ ,  $df = 7$ ,  $p < 0.001$ ) and  $Sx_{is}$  sequence pairs ( $\chi^2 = 91.029$ ,  $df = 43$ ,  $p < 0.001$ ) between these two groups. Table 4 presents the first occurring symptoms and symptom pairs with statistically significant odds for developing life-time dependence, followed by the significant single symptom and paired symptom patterns in which the odds favor not developing life-time dependence.

#### Non-dependent users

Among non-dependent cocaine-using subjects who reported at least one symptom, 27 of the 56 (i.e.  ${}_8P_2$ ) possible permutations of  $Sx_{is}$  were observed. The seven most frequent  $Sx_{is}$  sequences accounted for nearly 75% of the cases. The three most common sequences were  $Sx_{is} = 6$  then 4,  $Sx_{is} = 4$  then 1, and  $Sx_{is} = 6$  followed by 7.

#### Dependent users

Among subjects with a diagnosis of life-time cocaine dependence, 40 of the possible 56 two-symptom (i.e.  $Sx_{is}$ ) sequences were observed; the 12 most prevalent sequences accounted for nearly 75% of the cases. The three most frequently observed sequences were  $Sx_{is} = 76$ ,  $Sx_{is} = 64$  and  $Sx_{is} = 87$ . For permutations of three or more symptoms, 97 of the possible 336 (i.e.  ${}_8P_3$ )  $Sx_{fst}$  sequences were observed; the 32 most common sequences accounted for nearly 75% of the cases. For dependent users, the most frequently observed temporal patterns comprised of three symptoms were  $Sx_{fst} = 765$ ,  $Sx_{fst} = 876$  and  $Sx_{fst} = 642$ . Of the possible 1680 (i.e.  ${}_8P_4$ ) four-symptom sequences (i.e.  $Sx_{fst}$ ) 101 were observed, with the 36 most prevalent sequences accounting for nearly 75% of the subjects. The three  $Sx_{fst}$  sequences with the

**Table 5** Mean life-time total symptoms stratified by the presence or absence of particular symptoms or symptom sequences.

Sx presence or absence (~)	n	Mean total symptoms	SE of mean difference	(df = 42)
S <sub>x<sub>f</sub></sub> = 1	21	1.80	0.34	-5.68****
S <sub>x<sub>f</sub></sub> = ~1	402	3.73		
S <sub>x<sub>s</sub></sub> = 1	48	2.83	0.30	-6.20****
S <sub>x<sub>s</sub></sub> = ~1	279	4.68		
S <sub>x<sub>f<sub>s</sub></sub></sub> = 41	23	2.95	0.49	-3.20**
S <sub>x<sub>f<sub>s</sub></sub></sub> = ~41	303	4.52		
S <sub>x<sub>s</sub></sub> = 7	76	4.67	0.43	2.94**
S <sub>x<sub>s</sub></sub> = ~7	347	3.40		
S <sub>x<sub>s</sub></sub> = 8	24	5.83		
S <sub>x<sub>s</sub></sub> = ~8	302	4.30	0.55	2.80**
S <sub>x<sub>f<sub>s</sub></sub></sub> = 76	38	5.96	0.31	5.67****
S <sub>x<sub>f<sub>s</sub></sub></sub> = ~76	288	4.20		
S <sub>x<sub>f<sub>s</sub></sub></sub> = 87	23	5.92	0.67	2.44*
S <sub>x<sub>f<sub>s</sub></sub></sub> = ~87	303	4.30		

\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ; \*\*\*\* $p < 0.0001$ .

highest frequency were  $S_{x_{fstl}} = 7654$ ,  $S_{x_{fstl}} = 6421$  and  $S_{x_{fstl}} = 8765$ .

Since Table 4 presents the statistically significant single symptom and paired sequences related to dependence, Table 2 provides a comprehensive compendium of the percent of respondents reporting the most prevalent sequences among both dependent and non-dependent cocaine users.

#### Temporal symptom patterns: increasing the likelihood of cocaine dependence

As expected, among cocaine users several temporal symptom patterns increased the likelihood of developing life-time cocaine dependence. Subjects whose first symptom was physiological tolerance ( $S_{x_f} = 7$ ) were nearly five times *more likely* to become cocaine-dependent. When tolerance is followed immediately by continued use, despite knowledge of having a problem, the odds increase to nearly 20 times *more likely*. When withdrawal symptoms occur as the first symptom ( $S_{x_f} = 8$ ), the odds ratio of developing cocaine dependence is three times *more likely*. When subjects' first symptom is withdrawal and they experience physiological tolerance as the second symptom ( $S_{x_s} = 87$ ), they are 16.7 times *more likely* to become dependent than other life-time cocaine users. As Table 5 illustrates, subjects with the temporal symptom sequences of  $S_{x_f} = 7$ ,  $S_{x_s} = 8$ ,  $S_{x_{fs}} = 76$  or  $S_{x_{fs}} = 87$  have significantly more total life-time symptoms than other subjects.

#### Temporal symptom patterns: decreasing the likelihood of cocaine dependence

Subjects whose first or second reported symptom is 'using cocaine in larger amounts or for a longer period than

intended' (i.e.  $S_{x_f} = 1$  or  $S_{x_s} = 1$ ) are over four times *less likely* to develop life-time cocaine dependence than other subjects. Similarly, having frequent interference with social obligations as the earliest onset symptom ( $S_{x_f} = 4$ ) serves to decrease the likelihood of satisfying DSM-III-R criteria for cocaine dependence. The role of  $S_{x_f} = 4$  in limiting the likelihood of developing cocaine dependence is enhanced when the second symptom to emerge is the 'use of cocaine in larger amounts or for longer periods than intended' ( $S_{x_s} = 1$ ). Thus, subjects with the symptom sequence of  $S_{x_{fs}} = 41$  are more than seven times *less likely* to develop dependence relative to cocaine users with other  $S_{x_{fs}}$  sequences. As Table 5 reveals, in addition to being a factor that reduces the likelihood of developing cocaine dependence, subjects with  $S_{x_f} = 1$ ,  $S_{x_s} = 1$  or  $S_{x_{fs}} = 41$  have significantly fewer total life-time symptoms compared to cocaine users with other sequences.

#### Temporal symptom patterns: the order and occurrence of comorbid psychiatric disorders

Table 6 summarizes the relationships between symptom sequences and the presence or absence of 17 comorbid psychiatric diagnoses among cocaine users. Each of these 17 disorders was associated significantly with  $S_{x_f}$  or  $S_{x_s}$ ; 10 of the psychiatric disorders are associated significantly with both  $S_{x_f}$  and  $S_{x_s}$ . In particular, the presence or absence of comorbid alcohol abuse, alcohol dependence, dysthymia and panic disorder is associated with the temporal order in which cocaine dependence symptoms occur. Comorbid agoraphobia and mania show the weakest associations with temporal symptom sequences.

Table 7 indicates the temporal position of comorbid psychiatric disorders in relation to onset of cocaine

**Table 6** Association between symptom sequences and comorbid disorders.

	$Sx_i$ associated with comorbidity? (df = 7)	$Sx_{is}$ associated with comorbidity?
Adult antisocial		Yes***†
Agoraphobia <sup>1</sup>	No	Yes*†
Alcohol abuse <sup>2</sup>	Yes***	Yes***†
Alcohol dependence	Yes***	Yes***†
ASP <sup>3</sup>	No	Yes**†
Bipolar <sup>3</sup>	Yes *	Yes*†
Conduct disorder	No	Yes*†
Depression <sup>3</sup>	Yes*	Yes***†
Dysthymia <sup>3</sup>	Yes*	Yes***†
GAD <sup>3</sup>	Yes*	Yes***†
Mania <sup>3</sup>	No	No†
NAP	Yes**	Yes***†
Panic attack	Yes**	Yes***†
Panic disorder	Yes*	Yes***†
PTSD	Yes***	Yes***†
Simple phobia	No	Yes*†
Social phobia	No	Yes***†

<sup>1</sup> Agoraphobia without panic disorder.<sup>2</sup> Alcohol abuse with or without life-time dependence.<sup>3</sup> Without hierarchy.\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

† df = 37; ‡ df = 38.

use. For most cocaine users with a life-time history of comorbid disorders, the disorder precedes the onset of cocaine use. In particular, significantly more cocaine users with agoraphobia ( $\chi^2 = 33$ ,  $df = 1$ ,  $p < 0.001$ ), alcohol abuse ( $\chi^2 = 273$ ,  $df = 1$ ,  $p < 0.001$ ), alcohol dependence ( $\chi^2 = 74$ ,  $df = 1$ ,  $p < 0.001$ ), depression ( $\chi^2 = 13$ ,  $df = 1$ ,  $p < 0.001$ ), PTSD ( $\chi^2 = 38$ ,  $df = 1$ ,  $p < 0.001$ ), simple phobia ( $\chi^2 = 70$ ,  $df = 1$ ,  $p < 0.001$ ) and social phobia ( $\chi^2 = 119$ ,  $df = 1$ ,  $p < 0.001$ ) meet DSM-III-R criteria for one of these diagnoses prior to their first use of cocaine.

The temporal occurrence of these disorders in relation to the first use of cocaine was significantly associated with the cocaine dependence symptom sequences for each disorder, with the exception of social phobia. The relationship between the temporal sequence of onset of use and comorbidity is strongest for certain anxiety disorders (i.e. general anxiety disorder, panic attacks and simple phobia), and alcohol abuse.

## DISCUSSION

The results of this study reveal that the vast majority of life-time cocaine users did not develop dependence. Like alcohol users, cocaine users follow a limited array of symptom sequence pathways from first use to depend-

**Table 7** Association between symptom sequences and comorbid disorders.

	% Disorder precedes cocaine use onset (N)	% Disorder concurrent with cocaine use onset (N)	% Disorder follows cocaine use onset (N)	$Sx_f$ associated with order of comorbidity? (No = not significant)	$Sx_{fs}$ associated with order of comorbidity? (No = not significant)
Adult antisocial	N/A <sup>1</sup>				
Agoraphobia	74.5 (90)	0.0 (0)	25.5 (31)	No	Yes ( $\chi^2 = 28.11$ , $df = 12$ )**
Alcohol abuse	67.5 (491)	12.9 (94)	19.7 (143)	No	Yes ( $\chi^2 = 120.62$ , $df = 58$ )***
Alcohol depend.	52.0 (264)	17.5 (89)	30.5 (155)	Yes ( $\chi^2 = 24.53$ , $df = 14$ )*	Yes ( $\chi^2 = 93.67$ , $df = 54$ )**
ASP	N/A <sup>1</sup>	N/A <sup>1</sup>	N/A <sup>1</sup>		
Bipolar					
Conduct disorder					
Depression	53.3 (181)	8.5 (29)	38.2 (130)	No	Yes ( $\chi^2 = 83.88$ , $df = 52$ )**
Dysthymia	41.1 (56)	15.3 (20)	42.9 (57)	No	Yes ( $\chi^2 = 55.91$ , $df = 32$ )**
GAD	45.7 (56)	3.6 (4)	50.7 (62)	No	Yes ( $\chi^2 = 69.27$ , $df = 24$ )***
Mania	45.0 (39)	1.0 (2)	53.1 (47)	No	Yes ( $\chi^2 = 24.00$ , $df = 12$ )**
NAP	57.8 (4)	0.0 (0)	42.2 (3)	N/A <sup>2</sup>	
Panic attack	53.6 (84)	6.0 (9)	40.4 (63)	No	Yes ( $\chi^2 = 73.49$ , $df = 36$ )***
Panic disorder	48.1 (32)	0.0 (0)	51.9 (35)	Yes ( $\chi^2 = 11.63$ , $df = 5$ )*	No
PTSD	67.9 (102)	4.8 (7)	27.3 (41)	No	Yes ( $\chi^2 = 62.77$ , $df = 34$ )**
Simple phobia	79.8 (148)	2.5 (5)	17.7 (33)	Yes ( $\chi^2 = 26.27$ , $df = 12$ )*	Yes ( $\chi^2 = 55.45$ , $df = 19$ )***
Social phobia	86.9 (185)	0.4 (1)	12.7 (27)	No	No

<sup>1</sup> NCS time-related data is unavailable for this disorder.<sup>2</sup> Low base prevalence precludes analysis.\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

ence. In addition, distinct symptom sequences reduce the likelihood of developing cocaine dependence among life-time cocaine users. The premorbid incidence of tolerance and/or physiological withdrawal symptoms significantly increases the risk of developing cocaine dependence. The early occurrence of these symptoms might serve to permit the eventual development of cocaine dependence, if not encourage it. Alternatively, when it appears early in the temporal sequence of symptoms, rather than expediting the path to cocaine dependence, using cocaine 'in larger amounts or for longer than intended' is a symptom that mitigates against the development of life-time cocaine dependence. Similarly, experiencing 'frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, home' also diminishes the likelihood of developing cocaine dependence. The premorbid (i.e. predependence) occurrence of these two symptoms might act as a braking mechanism that obstructs or inhibits the pathway to developing a cocaine dependence disorder. The nature of this research does not permit us to conclude that these symptom pattern-disorder relationships are causal; the symptom patterns reported above are associated only with the increased or decreased likelihood of developing cocaine dependence. Obviously, the best way of assuring that one will not become cocaine-dependent is to avoid using cocaine.

A substantive difference distinguishes risk-enhancing from risk-diminishing symptoms: the risk-enhancing symptom pattern, withdrawal and tolerance, represents adaptive changes in the bodily systems affected by the intake of cocaine. Typically, these phenomena are subjective and only drug users can discern an advance of these symptoms. Alternatively, the risk-diminishing symptom patterns involve behaviors that are observable by others (e.g. loss of control over amount/duration of use and interference with normal responsibilities) and occur within a proximate social system. The admonitions of family, friends or co-workers might serve as a social feedback mechanism that is essential to limit setting and preventing the development of additional symptoms that lead eventually to dependent states.

#### **The relationship between psychiatric comorbidity and cocaine dependence symptoms**

Cocaine use both preceded and followed the presence of psychiatric comorbidity. However, more often than not psychiatric comorbidity precedes the use of cocaine. Like alcohol (Kessler *et al.* 1996; Nelson *et al.* 1998), cocaine use follows disproportionately a number of comorbid psychiatric conditions. Prospective research is necessary to determine whether these relationships are causal or

simply associative. In addition, variables not included in this study may be responsible for the emergence of both psychiatric comorbidity and cocaine-using patterns.

#### **Caveats**

The present study considers only eight of the nine category A DSM-III-R diagnostic criteria; although prevalence data are available for the ninth symptom (i.e. the use of a substance to alleviate withdrawal symptoms), the data needed to place this symptom in a temporal sequence were not available. This ninth symptom has attributes similar to the identified risk-enhancing predictors of dependence. Consequently, had these data been available it is possible that it would also have predicted an increased risk for the development of cocaine dependence as was observed for symptom eight. Since this additional symptom is essentially neuroadaptive, had it been included it might have increased further the confidence with which we consider these types of symptoms to increase the risk for developing cocaine dependence. Further, since category B DSM-III-R criteria did not add to our understanding of symptom onset, we excluded them from our sequencing analyses (B symptoms were used to create diagnoses). However, the symptom duration and frequency information provided by criterion B might be useful in future research that focuses on the impact of symptom duration and frequency of occurrence.

Respondents to the NCS interviews provided self-report of the symptoms and sequences of symptoms they experienced. Further, when interviewers asked about drug-related symptoms, respondents needed to remember which drugs were used and therefore had to keep in mind which drugs were associated with which symptoms. Like other retrospective data, this procedure provides an opportunity for memory distortion. Retrospective data are subject to memory distortion (e.g. Schacter 1995). Although Wittchen *et al.* (1989) have demonstrated the reliability of time-related symptom questions, this influence nevertheless holds the potential to bias the recollection of temporal sequences. Consequently, prospective data are necessary to clarify the causal relationships implied among the variables included in this cross-sectional evidence.

#### **Implications for clinicians**

By improving their understanding of drug use-related symptoms and the temporal progression of these symptoms, clinicians might be able to improve their capacity for treatment matching. Understanding the temporal sequencing of symptoms can also assist clinicians in

determining the extent of risks associated with continued pre-morbid drug use. In addition, clinicians can enhance screening and assessment activities, as well as the use of screening instruments, by examining carefully the sequence of reported symptoms. We encourage clinicians to develop evaluation instruments that specifically ask patients to sequence their cocaine use related symptoms temporally. Taken together, these advances could allow primary care providers to assess the severity and probable outcome of a patient's self-reported drug use. These devices could prove valuable in helping health-care providers match patients of different risk profiles with the treatments that will best serve their particular subtype of cocaine use.

Clinicians also will find it useful to recognize the comorbid conditions that might accompany cocaine use. These disorders can increase or decrease the risk of cocaine dependence. By understanding both the sequence of cocaine-related symptoms and the comorbid conditions that increase the risk of cocaine dependence, clinicians can improve treatment planning and matching options to minimize a patient's progression to cocaine dependence.

#### Future directions

It is beyond the scope of the present study to suggest, based solely on temporal sequencing of symptoms, that we should create a new typology of cocaine user. However, the current findings encourage future investigators to examine how symptom patterns inform extant typologies of substance users, such as those based on personality traits, level of psychological dependence, frequency of antisocial consequences, the presence of guilt and fear and age of onset (Cloninger 1987; Babor *et al.* 1992). Although scientists developed this typological strategy originally to distinguish subgroups of alcoholics, the approach is equally applicable to cocaine users (Ball *et al.* 1995). Since this research identified neuroadaptive symptoms that were associated with an increased risk for cocaine dependence compared with social symptoms that were linked to a lowered risk, the potential for the development of a cocaine user typology is promising.

When committees convene to draft new sets of diagnostic criteria, the temporal sequencing of symptoms might become an important technique through which the relative severity of a substance use disorder can be gauged. Previous research has demonstrated the inadequacy of merely counting the number of incident symptoms to determine severity (Weiss *et al.* 1992); perhaps symptom sequencing will provide an important supplement to the existing array of substance abuse assessment tools.

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