Longitudinal Relationship Between Psychological Distress and Multiple Substance Use: Results From a Three-Year Multisite Natural-History Study of Rural Stimulant Users*

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ABSTRACT. Objective: Substance use is associated with poor mental health, but little is known regarding how use of multiple substances is associated with mental health, particularly longitudinally, in community studies. This article examines this issue in a large ($N = 710$), natural-history study of rural stimulant (cocaine and/or methamphetamine) users in three states. **Method:** Respondent-driven sampling recruited recent (past-30-day) stimulant users in three counties each in Arkansas, Kentucky, and Ohio. Participants were interviewed every 6 months for 3 years. Mental health was measured by the Brief Symptom Inventory, and prior 6 months' substance use was measured for 17 possible substances. Data analysis used generalized estimating equations for longitudinal data with the Global Severity Index of the Brief Symptom Inventory as the dependent variable at each interview and substance use as predictor variables measured by number of substances used in the past 6 months and,

separately, the 17 individual substances, adjusting for use of substance-use treatment, demographics, and recruitment site. **Results:** On average, both Global Severity Index score and use of many substances declined over the course of study. Global Severity Index score was significantly associated with (a) greater number of substances used in the past 6 months ($p < .0001$) and (b) use of crack cocaine, methamphetamine, and nonprescription use of prescription painkillers and tranquilizers. **Conclusions:** Multiple and specific substances appear to incrementally increase psychological distress. Users of cocaine and methamphetamine are present in rural areas; these associations with poor psychological health raise concerns regarding availability of local treatment services for individuals with mental-health problems, as well as substance abuse. (*J. Stud. Alcohol Drugs*, 71, 258-267, 2010)

WIDESPREAD USE OF METHAMPHETAMINE and cocaine has become a recent phenomenon in many rural areas of the United States, with some rural states overwhelmed dealing with the legal consequences and treatment needs of methamphetamine use and production, and others identifying substantial cocaine use, cocaine trafficking, and need for cocaine treatment capacity and criminal justice involvement. Although much attention has been focused on criminal justice, treatment needs, and issues such as child welfare, less attention has been paid to the mental-health aspects of this rural stimulant use. Approximately a quarter of the U.S. general population meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994), criteria for a mental disorder, including substance-use disorders (Kessler et al., 2005), and

every national community epidemiologic study has shown that the odds of comorbid mental disorder are elevated among drug-dependent individuals (Conway et al., 2006; Kessler et al., 2005). Substance use is known to exacerbate psychiatric symptoms (Buckner and Mandell, 1990; Curran et al., 2002) and disorders (Curran et al., 2003; Saatcioglu et al., 2008)—including increased risk of relapse, multiple hospitalizations, loss of productivity, negative quality of life, and early mortality—and to impair a person's ability to access and adhere to treatment services (Curran et al., 2002; Phillips and Johnson, 2001).

However, our understanding of the relationship of substance use with mental-health symptoms or diagnoses is hampered by limited knowledge of the impact of multiple substance use. Many drug users use an array of both licit

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and illicit drugs, although usually they have a single “drug of choice” (Brecht et al., 2008; Kedia et al., 2007). Previous research has generally focused on one or two substances or psychiatric disorders/symptomatology only. For example, alcohol-use disorders are associated with increased rates of affective and anxiety disorders (Degenhardt et al., 2001; Grant et al., 2004), and marijuana use is associated with depression (Crome, 2007). Cocaine use and cocaine-use disorders have been linked to various psychiatric disorders (Conway et al., 2006; Tang et al., 2007) and symptoms (Falck et al., 2002), including co-occurring antisocial personality disorder, major depression, and anxiety disorders. Similarly, methamphetamine use and abuse are associated with various psychiatric disorders (Glasner-Edwards et al., 2008; Reiber et al., 2000) and symptoms (McKetin et al., 2006; Zweben et al., 2004), including depression and psychosis. Depression, hallucinations, and suicidal ideation have been reported to be particularly problematic among injection methamphetamine users, compared with noninjection users (Domier et al., 2000). Methamphetamine users have been shown to have higher rates of problems with hallucinations and depression, compared with cocaine users (Rawson et al., 2000).

Other than national single-wave or two-wave community epidemiologic surveys, such as the National Epidemiologic Survey on Alcohol and Related Conditions (Grant et al., 2004) and the National Comorbidity study (Kessler et al., 2005), the majority of comorbidity research has been conducted within clinical populations (Bakken et al., 2007; Schmitz et al., 2000) and not longitudinally. These national community studies have provided substantial information on changes between a baseline and single follow-up; however, they do not provide information on the trajectory of substance use and mental health (either psychiatric disorders or psychological symptoms) over multiple interviews.

Measurement of multiple substance use is a challenge in ascertaining the relationship between substance abuse and mental health (Crome, 2007). Multiple mental-health issues can be relatively easily summarized via a general symptom scale, such as the Symptom Check List (Haver, 1997; Sander and Jux, 2006) or its shorter Brief Symptom Inventory (BSI; Derogatis, 1993), both of which have a summary measure of psychological distress, the Global Severity Index (GSI). Measures of multiple drug use do not easily lend themselves to summary, in part because of the lack of consensus among comorbidity researchers about methodologies. To assess substance use comorbid with mental-health symptoms, researchers have relied on the Drug Use Composite of the Addiction Severity Index (McLellan et al., 1992) or a count of substances used with a measure of the frequency of use during the observation period (Brecht et al., 2008; Kedia et al., 2007). However, it is not clear what are the most useful measures of multiple substance use for examining mental-health issues, and this article examines several measurements. We

used Schensul and colleagues’ (2005) restriction of the term “polydrug use” to refer to drug mixing—that is, two or more drugs used during a brief period, usually 4 hours or less, and the term “multiple substance use or abuse” to describe the use of more than one substance during the reporting period wherein we lack data about possible concurrent drug mixing.

The purpose of this research was to examine the longitudinal relationship between mental-health symptoms or psychological distress as measured by the GSI score of the BSI and multiple substance use over the course of a 3-year natural-history study of rural stimulant (cocaine and methamphetamine) users. In particular, we were interested in understanding the relative contribution of specific substances (e.g., alcohol, marijuana, cocaine, methamphetamine, and nonprescription use of prescription painkillers and tranquilizers), as well as various specific measures of multiple substance use to psychological distress over time. The 710 participants used a range of different substances, and we were also interested in the relationship between changes in substance use and changes in GSI scores.

Method

Sample

Data are from a natural-history study of 710 stimulant users residing in rural counties of Arkansas, Kentucky, and Ohio (Booth et al., 2006). Counties were classified as rural according to the U.S. Office of Management and Budget definition of a nonmetropolitan county, that is, a county with a population of 50,000 or fewer persons. In addition to being rural, the counties were selected according to manageable driving distance from the researchers’ universities, location contiguous to or near other recruiting counties, and signs of local cocaine and/or methamphetamine use. Participant eligibility criteria included (a) not being in formal drug-abuse treatment within the past 30 days, (b) being 18 years of age or older, (c) using crack or powder form of cocaine and/or methamphetamine by any route of administration in the past 30 days, and (d) having a verifiable address within one of the study counties.

Participants were recruited using respondent-driven sampling, a variant of snowball sampling (Heckathorn, 1997; Wang et al., 2004). Study staff members recruited potential seeds through meeting drug-treatment providers, distributing research study business cards to persons who knew drug users, and visiting gathering places such as bars and county fairs (Draus et al., 2005). Study seeds who completed the baseline interview were asked to give referral coupons to people they knew who used drugs. If referrals resulted in study contact, the seeds received \$10 per contact for up to three contacts, but up to six referrals were allowed. Subsequent participants also followed the same procedures. Specific study eligibility criteria were not communicated

to avoid ineligible subjects “faking” criteria to obtain study remuneration. Confidentiality was maintained by requiring that potential study participants initiate study contact.

All participants completed the informed consent process, and written consent was obtained before the baseline interview. The study was approved by the pertinent institutional review boards of the investigators’ universities, and the researchers received a Certificate of Confidentiality from the National Institute on Drug Abuse. Trained research assistants conducted face-to-face baseline interviews using computer-assisted personal interview software on a laptop computer. Follow-up interviews were conducted at 6-month intervals for the next 36 months. At each follow-up interview, the majority of questions contained in the baseline interview were repeated, and urinalysis was conducted to help increase the veracity of self-reported drug use (Hamid et al., 1999; Hser, 1997). Extensive tracking information was obtained at the baseline interview and throughout all follow-up interviews so that participants could be relocated, culminating in a 73% follow-up participation rate at the 36-month interview.

We conducted extensive attrition analysis, comparing pairs of interviews to identify potential biased follow-up (data available from the first author). We found the largest attrition between baseline and 6 months (85% of baseline); attrition was greater for younger individuals, Whites, men, unmarried individuals, and those with higher incomes. We also found some later sporadic differential attrition for Whites, younger individuals, and those with higher incomes. Participants reporting nonprescription use of painkillers were less likely to participate in some interviews, and there were small differences in the number of substances used across a couple of interview pairs. Overall attrition at the 36-month interview varied somewhat among the users of specific substances at baseline, ranging from 26% of alcohol users to 35%-36% of users of painkillers and heroin. The only baseline substance outside this range was for users of Ecstasy, of whom 43% did not participate in the last interview, but only 10% of participants reported any use of this drug at baseline.

Measures

Brief Symptom Inventory. Recent (past-week) psychological distress was measured by the BSI (Derogatis, 1993), consisting of 53 items rated on a 5-point scale (0-4) with 0 indicating *no distress* and 4 indicating *extreme distress*. The BSI assesses nine symptom dimensions and provides a summary index of distress, the GSI. We have previously reported that mean GSI and subscale scores at baseline were substantially higher compared with general population norms (Booth et al., 2006). For this article, we used the GSI scores only (note that higher GSI score indicates greater psychological distress).

Demographic correlates. Age, gender, race (White or not), marital status, employment status, education (high

school graduate or not), and income (annual income $\geq$ \$10,000 or not) were used.

Substance use. Each interview (baseline and all follow-up interviews) contained a “drug matrix” developed by the Wright State University investigators for lifetime and recent use of a range of 17 substances: alcohol, marijuana, powder cocaine, crack cocaine, methamphetamine, heroin, oxycodone (OxyContin), nonprescription use of prescription painkillers, pharmaceutical methamphetamine (e.g., Desoxyn), methylphenidate (Ritalin), amphetamines, nonprescription use of prescription tranquilizers, 3,4-methylenedioxymethamphetamine (MDMA, or Ecstasy), ketamine, phencyclidine (PCP), lysergic acid diethylamide (LSD, or “acid”), and inhalants. For each substance, the interview queried whether used in lifetime; if lifetime use was endorsed, the interview queried (a) use (yes/no) during the past 6 months and (b) number of days used in the previous 30 days.

Data analysis. We first examined changes between consecutive pairs of interviews for individual substance use using McNemar’s tests and for GSI scores between individual substances using paired *t* tests. In addition, we examined changes over time in self-reports of individual substances, as well as bivariate differences in GSI by the individual substances at each interview using Wilcoxon rank-sum tests. We calculated frequencies of combinations of individual substances reported in the past 6 months (without inferring that these substances were used simultaneously), as well as a count of the 17 possible drugs reported in the previous 6 months. We also conducted exploratory analyses for injection drug use as a correlate of higher GSI, in which injection was reported as the most frequent route for any of the possible drugs. In all these and subsequent analyses, we set α at a conservative .01 because of the large sample size to reduce the chance of Type I error.

We used multivariate generalized estimating equations to examine whether changes in substance use were associated with changes in GSI score and whether differences in substance use were associated with GSI score (i.e., both within-subjects and between-subjects effects). Because GSI score was positively skewed and approximated a gamma-distribution after a small rescaling, a generalized linear model with log-link was fit to test the association between GSI score and substance use controlling for demographics. We adjusted for demographics and site, and whether substance-abuse treatment was received during the 3-year follow-up and the 3 years before baseline interviews (measured at each interview). Time was operationalized in linear form as 1-7 for the seven interviews. For analysis, we measured each substance as (a) use/no use in the previous 6 months and (a) number of days of use in the past 30 days. (Note that we use the term “substance” to include both illicit drugs and alcohol; we use the term “drugs” to refer to illicit drugs but not alcohol.) We dropped individual substances from models if they were both rarely used and nonsignificant when all

17 substances were included in multivariate models. Other models included the count of number of substances used in the previous 6 months.

Results

Description of sample

The overall sample at baseline has been described previously (Booth et al., 2006). Recruitment resulted in samples of 237 from Arkansas, 225 from Kentucky, and 248 from Ohio, for a total of 710. On average, the sample was male (61%), White (68%), not a high school graduate (61%), young ($M_{\text{age}} = 32.6$ years, $SD = 10.3$), and unemployed (68%). On average, the sample first used cocaine at age 21.3 years ($SD = 7.1$, range: 10-53) and methamphetamine at age 23 years ($SD = 8.3$, range: 9-54); and the sample reported use of 4.5 of 10 ($SD = 1.8$) substances at baseline. At baseline interview, 20.0% reported attending some form of substance-abuse treatment in the previous 3 years. At the 6 follow-up interviews, 6.5%, 7.4%, 8.3%, 9.8%, 9.1%, and 8.5% reported attending drug treatment in the previous 6 months at consecutive interviews.

Three-year trends in Global Severity Index

During the course of the 3-year follow-up, mean GSI score decreased significantly from baseline ($M = 0.9$, $SD = 0.7$) by almost 50% ($M = 0.5$, $SD = 0.7$) (Table 1), although the maximum scores stayed similar (approximately 3.5, compared with minimums of 0; data not reported). At the 36-month interview, the T score standardized to the general population was 56.85 ($SD = 21.71$); in other words, the T score approached general population norms in contrast to the baseline T score of 68.0 ($SD = 22.7$) (Table 1). All pairs of interviews from baseline through the 18-month interview differed significantly from scores at the next follow-up interview (paired t tests, all $ps < .05$), but there were no differences between the last two consecutive interviews at 24 and 36 months.

Trends in drug use

The self-report of past-6-month use for most substances decreased substantially over the 3 years (see Table 1). Of the most frequently used substances, large decreases were

TABLE 1. Changes in substance use and Global Severity Index (GSI) score over time

Variable	Baseline ($n = 710$) n (%)	6 months ($n = 603$) n (%)	12 months ($n = 581$) n (%)	18 months ($n = 575$) n (%)	24 months ($n = 561$) n (%)	30 months ($n = 563$) n (%)	36 months ($n = 519$) n (%)
Alcohol	620 (87.32)	522 (86.57)	492 (84.68)	468 (81.39)	464 (82.71)	456 (81.14)	407 (78.42)
Marijuana	603 (84.93)	501 (83.08)**	456 (78.49)	424 (73.74)	406 (72.37)	393 (69.80)	365 (70.33)
Powder cocaine	408 (57.46) [†]	253 (41.96)**	208 (35.80)	195 (33.91)	190 (33.87)**	155 (27.53)	135 (26.01)
Crack cocaine	464 (65.35) [†]	334 (55.39) [†]	274 (47.16)	247 (42.96)	239 (42.60)	237 (42.10)	212 (40.85)
Heroin	70 (9.86)	46 (7.63)	36 (6.20)**	22 (3.83)	38 (6.77)	33 (5.86)	25 (4.82)
Oxycodone	155 (21.86)**	93 (15.42)	67 (11.53)	68 (11.83)	73 (13.01)**	49 (8.70)	38 (7.32)
Nonprescription use of prescription painkillers	369 (52.12)**	263 (43.62)	229 (39.41)	205 (35.65)	191 (34.11)	172 (30.55)	150 (28.90)
Pharmaceutical methamphetamine	23 (3.24)	10 (1.66)	6 (1.03)	6 (1.04)	5 (0.89)	2 (0.36)	1 (0.19)
Nonpharmaceutical methamphetamine	344 (48.66) [†]	212 (35.16)**	180 (30.98) [†]	129 (22.43)	105 (18.72)	86 (15.28)	68 (13.10)
Methylphenidate	46 (6.48)	19 (3.15)	10 (1.72)	11 (1.91)	15 (2.67)	11 (1.95)	8 (1.54)
Amphetamine	118 (16.67)**	67 (11.11)**	37 (6.37)	35 (6.09)	24 (4.28)	19 (3.37)	12 (2.31)
Nonprescription use of prescription tranquilizers	239 (33.66)	202 (33.50)***	148 (25.47)	160 (27.83)	154 (27.45)	135 (23.98)	124 (23.94)
Ecstasy/MDMA	69 (9.72) [†]	23 (3.81)	19 (3.27)	17 (2.96)	21 (3.74)	22 (3.91)	19 (3.66)
Ketamine	33 (4.65)**	7 (1.16)	3 (0.52)	4 (0.70)	1 (0.18)	1 (0.18)	1 (0.19)
PCP/angel dust	14 (1.97)	3 (0.50)	2 (0.34)	1 (0.17)	0 (0.00)	1 (0.18)	0 (0.00)
LSD ("acid")	63 (8.87) [†]	15 (2.49)	12 (2.07)	21 (3.65)	16 (2.85)	8 (1.42)	4 (0.77)
Inhalants	27 (3.81)	15 (2.49)	13 (2.24)	6 (1.04)	6 (1.07)	9 (1.60)	9 (1.73)
# substances used, M (SD)	5.16 (2.58) [†]	4.29 (2.25) [†]	3.77 (2.12)***	3.51 (2.12)	3.47 (2.19)***	3.18 (2.05)**	3.04 (1.95)
Standardized T score for GSI, general population, M (SD)	68.00 (22.68) [†]	64.72 (23.84)	61.77 (22.79) [†]	59.37 (21.58)	57.77 (21.33)	56.92 (20.88)	56.85 (21.71)

Notes: MDMA = 3,4-methylenedioxymethamphetamine; PCP = phencyclidine; LSD = lysergic acid diethylamide.

Significant difference between the interview where the superscript was placed and the interview immediately following: ** $p < .01$; *** $p < .001$; [†] $p < .0001$.

found for powder cocaine, crack cocaine, nonprescription methamphetamine, and nonprescription use of prescription painkillers and tranquilizers. However, although use of al-

cohol and marijuana decreased, the declines were at a lesser rate (alcohol: 87.3%-78.4%, marijuana: 84.9%-70.3%). All individual substances significantly decreased over time (gen-

TABLE 2. Global Severity Index of the Brief Symptom Inventory score by individual substances in past 6 months, *M* (*SD*)

Variable	Baseline (<i>n</i> = 710)	6 months (<i>n</i> = 603)	12 months (<i>n</i> = 581)	18 months (<i>n</i> = 575)	24 months (<i>n</i> = 561)	30 months (<i>n</i> = 563)	36 months (<i>n</i> = 519)
Alcohol							
No	0.81 (0.66)	0.73 (0.77)	0.69 (0.69)	0.63 (0.75)	0.47 (0.66)	0.48 (0.62)	0.48 (0.67)
Yes	0.86 (0.71)	0.76 (0.74)	0.66 (0.71)	0.58 (0.65)	0.56 (0.66)	0.52 (0.65)	0.52 (0.68)
Marijuana							
No	0.73 (0.69)	0.58 (0.67)***	0.56 (0.70)**	0.50 (0.65)**	0.46 (0.59)	0.43 (0.57)	0.41 (0.63)**
Yes	0.88 (0.70)	0.79 (0.75)	0.69 (0.71)	0.62 (0.67)	0.57 (0.69)	0.55 (0.67)	0.56 (0.69)
Powder cocaine							
No	0.82 (0.72)	0.70 (0.74)**	0.63 (0.69)	0.57 (0.64)	0.51 (0.64)	0.47 (0.63)	0.45 (0.64)***
Yes	0.88 (0.69)	0.83 (0.73)	0.72 (0.73)	0.64 (0.72)	0.60 (0.70)	0.63 (0.69)	0.68 (0.75)
Crack cocaine							
No	0.73 (0.60)**	0.66 (0.71)**	0.62 (0.67)	0.51 (0.59)	0.50 (0.62)	0.44 (0.58)**	0.41 (0.56)**
Yes	0.93 (0.74)	0.83 (0.76)	0.72 (0.74)	0.70 (0.75)	0.60 (0.71)	0.62 (0.72)	0.65 (0.79)
Heroin							
No	0.83 (0.69)***	0.73 (0.74) [†]	0.64 (0.70) [†]	0.57 (0.66) [†]	0.53 (0.66)**	0.48 (0.63) [†]	0.48 (0.64) [†]
Yes	1.15 (0.74)	1.07 (0.68)	1.03 (0.68)	1.11 (0.76)	0.71 (0.65)	1.03 (0.72)	1.23 (0.88)
Oxycodone							
No	0.78 (0.69) [†]	0.72 (0.73) [†]	0.62 (0.69) [†]	0.55 (0.66) [†]	0.49 (0.62) [†]	0.48 (0.64) [†]	0.47 (0.63) [†]
Yes	1.13 (0.68)	0.98 (0.75)	1.01 (0.74)	0.88 (0.69)	0.88 (0.80)	0.88 (0.59)	1.08 (0.88)
Nonprescription use of prescription painkillers							
No	0.64 (0.59) [†]	0.61 (0.71) [†]	0.52 (0.61) [†]	0.49 (0.61) [†]	0.44 (0.59) [†]	0.43 (0.60) [†]	0.41 (0.58) [†]
Yes	1.06 (0.74)	0.94 (0.73)	0.89 (0.78)	0.77 (0.73)	0.73 (0.75)	0.71 (0.70)	0.76 (0.80)
Prescription methamphetamine							
No	0.84 (0.69)**	0.76 (0.74)	0.66 (0.71)	0.59 (0.67)	0.54 (0.66)	0.51 (0.64)	0.51 (0.67)
Yes	1.39 (0.87)	0.59 (0.45)	0.84 (0.79)	0.55 (0.49)	0.64 (0.68)	1.49 (2.00)	2.68 (–) ^a
Nonprescription methamphetamine							
No	0.79 (0.70)**	0.68 (0.72) [†]	0.58 (0.68) [†]	0.56 (0.64)	0.52 (0.63)	0.50 (0.65)	0.50 (0.66)
Yes	0.93 (0.70)	0.89 (0.76)	0.85 (0.72)	0.69 (0.75)	0.62 (0.77)	0.57 (0.62)	0.59 (0.74)
Methylphenidate							
No	0.84 (0.70)**	0.74 (0.73)**	0.66 (0.70)	0.58 (0.66)	0.53 (0.65)**	0.50 (0.64)**	0.50 (0.66)**
Yes	1.14 (0.69)	1.24 (0.83)	1.11 (0.77)	1.25 (0.85)	1.03 (0.75)	1.03 (0.86)	1.49 (1.02)
Amphetamine							
No	0.80 (0.69) [†]	0.72 (0.73) [†]	0.64 (0.70)***	0.58 (0.68)**	0.54 (0.66)	0.51 (0.64)	0.50 (0.66)
Yes	1.13 (0.69)	1.05 (0.76)	1.02 (0.73)	0.74 (0.54)	0.64 (0.66)	0.72 (0.90)	0.87 (1.02)
Nonprescription use of prescription tranquilizers							
No	0.72 (0.65) [†]	0.61 (0.66) [†]	0.57 (0.67) [†]	0.50 (0.62) [†]	0.45 (0.60) [†]	0.45 (0.62) [†]	0.42 (0.60) [†]
Yes	1.13 (0.72)	1.05 (0.80)	0.95 (0.72)	0.83 (0.73)	0.79 (0.75)	0.73 (0.68)	0.82 (0.80)
Ecstasy/MDMA							
No	0.84 (0.70)	0.76 (0.74)	0.67 (0.71)	0.59 (0.67)	0.54 (0.67)	0.51 (0.65)	0.52 (0.68)
Yes	1.00 (0.67)	0.77 (0.83)	0.50 (0.42)	0.59 (0.56)	0.48 (0.36)	0.53 (0.51)	0.41 (0.43)
Ketamine							
No	0.85 (0.71)**	0.75 (0.74)	0.66 (0.70)	0.59 (0.67)	0.54 (0.66)	0.51 (0.65)	0.51 (0.67)
Yes	1.09 (0.60)	1.18 (0.88)	2.03 (0.96)	0.88 (1.00)	0.81 (–) ^a	0.60 (–) ^a	1.62 (–) ^a
PCP							
No	0.85 (0.70)	0.76 (0.74)	0.67 (0.71)	0.59 (0.67)	0.54 (0.66)	0.51 (0.64)	0.51 (0.67)
Yes	1.19 (0.64)	0.85 (0.77)	0.24 (0.23)	1.57 (–) ^a		2.65 (–) ^a	
LSD ("acid")							
No	0.83 (0.70) [†]	0.75 (0.74)	0.66 (0.71)	0.58 (0.67)	0.54 (0.67)	0.51 (0.65)	0.51 (0.67)
Yes	1.18 (0.68)	1.02 (0.82)	0.83 (0.55)	0.81 (0.73)	0.52 (0.39)	0.53 (0.35)	0.73 (0.45)
Inhalants							
No	0.85 (0.70)	0.75 (0.74)	0.66 (0.71)	0.59 (0.67)	0.54 (0.66)	0.51 (0.65)	0.50 (0.67)**
Yes	1.05 (0.67)	1.07 (0.78)	0.91 (0.68)	0.93 (0.69)	0.62 (0.51)	0.82 (0.66)	0.94 (0.53)

Notes: MDMA = 3,4-methylenedioxymethamphetamine; PCP = phencyclidine; LSD = lysergic acid diethylamide. ^aStandard deviation could not be estimated because only one observation was present.

p* < .01; *p* < .001; [†]*p* < .0001 based on Wilcoxon rank-sum test for differences in Brief Symptom Inventory Global Severity Index between individual substance users and nonusers in the past 6 months at each interview.

eralized estimating equations [GEE] with a test for time, $p < .001$), except for use of inhalants. At the end of the 3-year follow-up, 7.3% of the 36-month participants reported no use of any substances, an additional 14.5% ($n = 77$) reported use of only one substance, and 20.2% ($n = 105$) reported use of only two substances (data not reported). Injection drug use for any drug also declined over the course of the study (data not reported), from 12.8% at baseline to 6.2% at the 36-month interview.

Overall, the multiplicity of substance use decreased over time from a mean of 5.2 substances ($SD = 2.6$) at baseline to 3.0 ($SD = 2$) at the 36-month interview. The most common drug-use combinations at baseline included alcohol, cocaine (including either crack and/or powder cocaine), and marijuana with or without other substances (67.0% at baseline but only 41.6% at the 36-month interview). Overall, the most frequent combinations involved these three plus one other

drug, most often methamphetamine or nonprescription use of tranquilizers or painkillers (data not reported).

Substance use and Global Severity Index: Bivariate results

We found significant differences in GSI score for use of many individual substances (see Table 2), particularly for users of heroin, nonprescription painkillers and tranquilizers, oxycodone, and crack cocaine. In many cases, the GSI average score for users was 50% greater than the score for nonusers of a particular substance. Using the count of the 17 separate individual substances, we also found an overall linear relationship between number of substances used and GSI score at each interview (Figure 1; note that we did not find any significant differences for GSI score between 0, 1, or 2 substances at any time interval). Furthermore, GSI appeared to decline across the lower levels of multiple sub-

FIGURE 1. Relationship between number of substances used in the previous 6 months (M) and mean Global Severity Index (GSI) score during 3 years of study (interviews from baseline through 36 months)

stance use over time. We also found a significant difference in GSI by injection drug use in five of seven interviews (data not reported).

Multivariate models

Overall, the variables measuring number of substances and time were highly significant predictors of GSI score ($p < .0001$) after adjusting for site and demographic variables (Table 3). There was no significant interaction between num-

ber of drugs and time, indicating that the association of number of drugs with GSI score stayed constant over the study. Other significant positive predictors of GSI score were older age ($p = .005$), female gender ($p < .0001$), income less than \$10,000 ($p = .002$), and study site. The variable measuring whether the participant had reported attending substance-abuse treatment was not significant.

In the model with individual substance-use variables (any self-reported use in the previous 6 months), as shown in Table 3, we found significant effects of methamphetamine

TABLE 3. Multivariate analysis of psychological distress and multiple substance use

Variable	Model with # of substances used (past 6 months)		Model with individual substance use (past 6 months)		Model with # days substance use (past 30 days)	
	Estimate	<i>p</i>	Estimate	<i>p</i>	Estimate	<i>p</i>
Time	-.0575	<.0001	-.0647	<.0001	-.0735	<.0001
# of substances used	.0696	<.0001				
Alcohol			.0278	.4607	.0001	.9306
Marijuana			.0744	.0454	.0028	.0363
Powder cocaine			.0456	.0767	.0047	.1639
Crack cocaine			.0756	.0119		
1-7 days					.0472	.1551
8-14 days					.1188	.0178
15-23 days					.1237	.0179
24-30 days					.2310	.0006
Heroin			.0474	.3821	.0070	.0497
Oxycodone			.0162	.6488	-.0005	.9101
Nonprescription use of painkillers			.1233	<.0001		
1-7 days					.0777	.1556
8-14 days					-.0465	.6424
15-23 days					.0303	.7408
24-30 days					-.0893	.4097
Time × Nonprescription Use of Painkillers						
Time × 1-7 days					-.1825	.0052
Time × 8-14 days					.0397	.1284
Time × 15-23 days					.0465	.0315
Time × 24-30 days					.0745	.0004
Nonpharmaceutical methamphetamine			.1000	.0030		
1-7 days					.0608	.1275
8-14 days					.1646	.0128
15-23 days					.1908	.0039
24-30 days					.4188	<.0001
Methylphenidate			.1173	.0551		
Amphetamine			-.0453	.2563	.0036	.3143
Nonprescription use of tranquilizers			.1422	<.0001	.0077	.0039
Ecstasy/MDMA			.0023	.9647	.0107	.4747
LSD ("acid")			.0636	.2187		
Inhalants			.1713	.0248		
Substance-abuse treatment	-.0411	.2892	-.0559	.1010	-.0296	.4037
Age	.0089	.0051	.0103	.0023	.0091	.0096
Male	-.2872	<.0001	-.2852	<.0001	-.2569	<.0001
White	.0466	.4945	.0107	.8825	.0608	.4173
Unmarried	-.0901	.1728	-.0765	.2642	-.0802	.2397
High school education	-.1156	.0388	-.1212	.0416	-.1120	.0582
Employed	-.0600	.3056	-.0611	.3252	-.0593	.3415
Annual income ≥ \$10,000	-.1932	.0020	-.1909	.0038	-.1885	.0044
State (reference: Ohio)						
Arkansas	-.4958	<.0001	-.5624	<.0001	-.6493	<.0001
Kentucky	-.0898	.1249	-.1406	.0314	-.1825	.0052

Notes: MDMA = 3,4-methylenedioxymethamphetamine; LSD = lysergic acid diethylamide.

($p = .003$) and nonprescription use of painkillers ($p < .0001$) and tranquilizers ($p < .0001$). For this model, we excluded three drugs that were very rarely used: prescription methamphetamine, ketamine, and PCP. In the model for days of substance use in the past 30 days, we eliminated prescription methamphetamine, ketamine, PCP, methylphenidate, LSD, and inhalants from the model because of very infrequent use. We found that a linear association did not fit for three of four significant variables (crack cocaine, methamphetamine, and nonprescription use of painkillers). Therefore, we categorized these substances in five categories (0 days, 1-7 days, 8-14 days, 15-23 days, and 24-30 days), with 0 days as the reference group. For methamphetamine and crack cocaine, only greater days of use (more than 14 days) were associated with the higher GSI score. Also, a significant interaction between time and painkiller days was also found (see Table 3), indicating that more days of painkiller use was significantly associated with GSI score in later interviews only. In exploratory GEE analysis for injection drug use reported for any drug, adjusting for demographic characteristics, we found that injection drug use was significant ($p < .05$, data not reported).

Discussion

Our longitudinal analysis shows strong associations between greater variety in substance use and increased psychological distress, as well as evidence that reductions in the number of multiple drugs used, as well as specific drugs, are associated with decreases in psychological distress, or improvements in mental health, even after adjusting for drug-treatment attendance. The direction of the relationship is, however, unclear because multiple drug use or specific drug use may indeed result in greater psychological distress, but certainly greater psychological distress could lead to greater multiple substance use as "self-medication." For example, methamphetamine users may turn to tranquilizers to mitigate the anxiety that may be a concomitant of the methamphetamine use. Others may use either tranquilizers or painkillers to dampen withdrawal symptoms.

We examined several ways to measure multiple substance use and have concluded that the most parsimonious model uses either number of separate substances used or indicators of separate substances, either as a dichotomous indicator or number of days of use. It is clear from our analyses that the array of potential substances used needs to be accounted for when investigating mental-health issues in a sample of substance users who are already using either cocaine or methamphetamine, given that a large majority of them were already multiple substance users with concurrent use at least of alcohol and marijuana at the beginning of the study. The multivariate analyses with the various individual substances consistently found strong independent effects for use of crack cocaine, methamphetamine, and nonprescription use

of painkillers and tranquilizers. In our study, crack cocaine was a strong correlate of psychological distress, but use of cocaine hydrochloride was not. This finding may be a consequence of more days of crack use compared with powder cocaine use (generally approximately 3:1 at each interview, data not reported), with more frequent crack use possibly associated with greater availability, lower cost, or simply crack-specific use patterns. Alcohol was neither a bivariate correlate nor an independent correlate of distress in multivariate analysis, an interesting finding given that research on substance-use/mental-health comorbidity has so focused on the relationship of alcohol to psychological distress and psychiatric comorbidity. Our results indicate that, at least in substance users already using stimulants, both stimulant use and misuse of prescription drugs are far more important correlates. Furthermore, nonuse of alcohol was relatively infrequent, which may be why we did not find an association.

In an earlier publication from the same cohort, we found that use of cocaine and methamphetamine decreased significantly over the first 2 years of follow-up (Borders et al., 2008). Our results presented here (see Table 1) found that use of most substances also decreased over the 3 years of the study as shown by a baseline mean count of five substances and a 36-month mean count of three substances. Furthermore, almost 10% of the 36-month sample (7.3%) reported no use of any substances, and another 14.5% reported use of only one substance, mainly alcohol. Use of both alcohol and marijuana declined at lower rates, which may reflect greater availability, fewer consequences if participants were trying to reduce consequences, or simply that many illicit drug users regard marijuana a nonproblematic drug similar to alcohol.

The decrease in methamphetamine use continued throughout the last year of follow-up, from 48.7% at baseline to only 13.1% at 36 months, although the greatest decline happened in the first 24 months of the follow-up period. In our previous paper, we found that decreases in methamphetamine use over the first 24 months were not associated with implementation of restrictions in precursor chemicals among the untreated subset of our study population (Borders et al., 2008). Interestingly, a qualitative report from 24 participants in the Arkansas and Kentucky samples found that health, legal, and family issues, or a combination of these factors, were linked to quitting or reducing methamphetamine use (Sexton et al., 2008).

We have observed declines in other observational studies (Booth et al., 2001, 2004; Falck et al., 2007; Thapa et al., 2007). Other longitudinal observational studies have also found similar portions of abstinent users (Chen and Kandel, 1995; Deren et al., 1999; Price et al., 2001). It is possible that our study methods, including comprehensive drug assessment and urinalysis at each follow-up interview for 3 years, as well as 2 hours of attention from research staff and contacts for follow-up appointments, may have acted as unmeasured interventions or a Hawthorne effect. Future

natural-history studies of substance users should begin to evaluate this issue. It is also possible that we were observing a "reversion to the mean," in which we identified participants at a peak in their drug-use trajectory from which they declined over the course of the study (Finney, 2008).

Because this study was not designed to assess the effectiveness of substance-abuse treatment, we adjusted only for treatment attendance over the course of the study, but did not carry out extensive analyses of treatment. However, treatment participation would also be expected to be associated with reduced substance use, which might then be associated with improved psychological distress. Our finding of a non-significant effect should not be interpreted as evidence of lack of effectiveness but rather of a need for further exploration, perhaps of a reduced sample of treatment attendees and examining proximal and distal outcomes following treatment. We also did not include attendance at mental-health services in our analysis, which might have led to differing findings.

One limitation to this study is in our measures of multiple substance use. We do not know whether individual substances were consumed in relationship to others, such as whether used concurrently, in place of another more usual substance, or immediately before or after another substance. Such information would be useful to understand more fully the issues of multiple substance use (Schensul et al., 2005). Furthermore, we only minimally addressed the issue of route of administration because of our focus on multiple substance use, although we did have one route of administration (crack vs. powder cocaine) that we explored more fully. There have been some prior indications that methamphetamine injection is associated with poor mental health (Domier et al., 2000), and our exploratory findings suggest that injection of any drug may be associated with higher GSI. However, further work needs to be done to develop this issue more fully.

Other limitations to this research include concerns with the effect of attrition. We found some evidence of differential attrition by individuals with multiple substance use and specific substance use (mainly misuse of prescription painkillers), although not consistently across all pairs of interviews. However, potential loss of individuals with these characteristics would probably bias estimation of the association between those variables and GSI score toward null findings rather than the reverse. Another limitation is that we used respondent-driven sampling instead of random sampling to obtain our sample, but random sampling is not feasible with hidden populations such as illicit drug users.

In conclusion, our finding of decreases in substance use with concomitant improvements in psychological distress is particularly important given uncertain access to treatment services in many rural areas. Further research needs to be undertaken to understand how and why these individuals are able to accomplish reductions in substance use without treatment. On the other hand, it is important to note that

we found an important subgroup who continued multiple substance use with associated higher levels of distress at the end of our study, a finding that is of concern given that many rural residents do not have access to clinical programs that focus on clients with both substance use and mental-health problems.

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