

Subjects reported that symptoms persisted for between five days and three weeks. Similar findings regarding the range of symptoms present following cessation of amphetamine use were reported by Churchill and colleagues.⁹ Because these interviews focused on the general features of the amphetamine abstinence syndrome, the time-course and severity of the symptoms were not characterized.

Srisurapanont and colleagues developed a scale to assess amphetamine withdrawal symptoms based primarily on *DSM IV*¹⁰ and then used this scale to document any change in withdrawal symptoms over time in subjects meeting *DSM IV* criteria for amphetamine withdrawal.¹¹ The scale consisted of eleven items identified in *DSM IV* as symptoms of amphetamine withdrawal. Following one to five days of withdrawal from amphetamine, decreased energy and an increased appetite and need for sleep were the predominant symptoms. In the separate longitudinal study,¹¹ scores on these items were elevated at entry and remained elevated at the end of two weeks, though any change in abstinence symptoms over time was not evaluated statistically. Further, because subjects not meeting *DSM IV* criteria for amphetamine withdrawal were excluded, the results apply only to a restricted range of amphetamine users.

We performed this study to systematically evaluate the severity and short-term course of symptoms characterizing the amphetamine abstinence syndrome employing a commonly used and validated measure, the Beck Depression Inventory (BDI).¹² Non-treatment-seeking volunteers were studied in order to avoid confounding the effects of treatment. One group of subjects was studied as inpatients during the first three days of initial abstinence, and the other group was studied as inpatients following eleven days of monitored outpatient abstinence. Including subjects with differing durations of abstinence

allowed for the estimation of the stability of self-reported symptoms.

METHODS

Participants

Participants included nineteen non-treatment-seeking, methamphetamine-dependent subjects recruited from the community through advertisements in local newspapers. Potential participants were excluded for a history of stroke, traumatic brain injury, epilepsy, or Axis I psychotic or mood disorders, or for testing HIV seropositive. Participants gave written informed consent after being apprised of the study risks and were reimbursed for participation. All subjects met *DSM IV* criteria for methamphetamine dependence using the SCID.¹³

Subjects reported using at least 0.5 grams of methamphetamine per week for the six months prior to the study and produced a positive methamphetamine urine sample prior to admission. The route of methamphetamine administration for these subjects included insufflation (snorting), smoking, and intravenous use. Although the use of other drugs was common, study participants primarily used methamphetamine and did not meet *DSM-IV* criteria for dependence on any other substance other than nicotine.

Two groups of subjects were evaluated: one group was hospitalized in order to achieve initial abstinence and then evaluated over Days 1–3 of abstinence and the other group abstained from methamphetamine use for eleven days as outpatients (as documented by urine toxicology) and was then evaluated during Days 12–14 of abstinence as inpatients. These groups are referred to as “early study entry” and “late study entry.” Group membership was determined on the basis of the participants’ choice.

Procedures

Individuals were administered a 2.5-hour battery of neurocognitive measures, the Structured Clinical Interview for *DSM-IV* (SCID-IV),¹³ the Addiction Severity Index (ASI),¹⁴ and the North American Adult Reading Test.¹⁵ The BDI¹² was administered daily. Results from the neurocognitive assessment battery have been described elsewhere.¹⁶ The intensity of symptoms attributed to methamphetamine withdrawal was assessed using the total score from the BDI.

Data Analysis

Demographic and drug use characteristics of the groups were compared using *t*-tests. Changes in depressive symptoms, indexed by the sum score of the BDI, was evaluated over time using a mixed model repeated measures ANOVA. The between-group measure was study group (early or late abstinence), and the within-group measure was the sum score on the BDI.

We then sought to identify items from the BDI that were persistently elevated during withdrawal. We utilized one-sample *t*-tests to identify those items that were most likely to be endorsed during the first three days of abstinence. Because we conducted *t*-tests for each item (21 per day), a family-wise correction procedure for multiple comparisons was used to adjust the *p* value to 0.01.¹⁷

RESULTS

The groups had similar demographic characteristics. Subjects in the early study entry group had a mean age of 33.4 years (range 26–49, SD 7.4). Eight subjects were male and three were female. Seven were Caucasian, three were Hispanic, and one was African-American. Subjects in the late study entry group had a mean age of 36.2 years

(range 26–49, SD 8.8). There were seven males and one female. Four were Caucasian, three were African-American, and one was Hispanic. The groups did not differ with regard to age, gender, or ethnicity ($p > .10$).

Subjects in the early study entry group reported using methamphetamine on 20.5 of the thirty days (average) before study entry (SD 7.8); in contrast, subjects in the late study entry group reported using methamphetamine on 8.4 of the thirty days (average) before study entry (SD = 8.9). The early study entry group used methamphetamine significantly more days during the month preceding study entry than the late study entry group ($t(17) = 3.17$, $p < .01$). The groups reported similar lifetime use histories, with the early study entry group reporting 9.4 years (SD 3.3) and the late study entry group reporting 12.4 years (SD 10.6) of methamphetamine use ($t(17) = .89$, $p = \text{NS}$). Six subjects reported using methamphetamine by the IV route in the early group, whereas three reported IV use in the late group. The groups had similar patterns of smoked, nasal, and oral use: both groups had two subjects that preferred smoking, the early group had three nasal users whereas the late group had two, and the late group had one oral user.

Because the groups differed on frequency of use during the thirty days prior to study entry, we examined the correlation between frequency of use and score on the BDI for each study day. These correlations were small and non-significant, eliminating the need to include frequency of use as a covariate in subsequent analyses.

A repeated measures ANOVA revealed that BDI scores decreased significantly over time ($F(2,16) = 6.7$, $p = .008$). Table 1 shows BDI ratings for the two groups studied during the three days of hospitalization. Individuals in the early study entry group tended to report mild to moderate levels of depressive symptoms during the first two days of abstinence (BDI > 11)¹⁸ and

TABLE 1. Beck Depression Inventory Sum Scores Over Three Days of Hospitalization

| Group | Day 1 Mean (SD) | Day 2 Mean (SD) | Day 3 Mean (SD) |
|-----------------------------------|-----------------|-----------------|-----------------|
| Early abstinence (<i>n</i> = 11) | 14.5 (8.1) | 11.4 (7.8) | 7.3 (8.1) |
| Late abstinence (<i>n</i> = 8) | 7.2 (5.4) | 7.5 (5.1) | 5.7 (4.4) |

Levels of depression fell over the three days of hospitalization ($F(2,16) = 6.7, p = .008$). This was more evident in the group assessed during early abstinence.

minimal levels on the third day. Individuals in the late study entry group tended to report minimal levels of depression throughout their participation in the study, with scores declining over the course of the study. The interaction of day \times group approached significance ($F(2,16) = 2.7, p < .10$), indicating that BDI scores in the early group tended to decrease at a greater rate than did those in the late group.

There was a greater range of depressive symptoms in the early abstinence group compared to the late abstinence group (Figs. 1 and 2). In the early group, seven, six, and four subjects reported mild to

moderate levels of self-reported depressive symptoms on Days 1–3, respectively. Only one subject in the late abstinence group had a BDI score greater than 11 over any of the three days. Conversely, by Day 3, seven subjects in the early abstinence group had minimal levels of depression (BDI below 4), whereas four subjects had BDI scores of 11 or greater.

Responses on individual items from the BDI were examined in the early abstinence group in order to better identify symptoms that were most prominent during early abstinence. Responses on three items were statistically different from 0 on

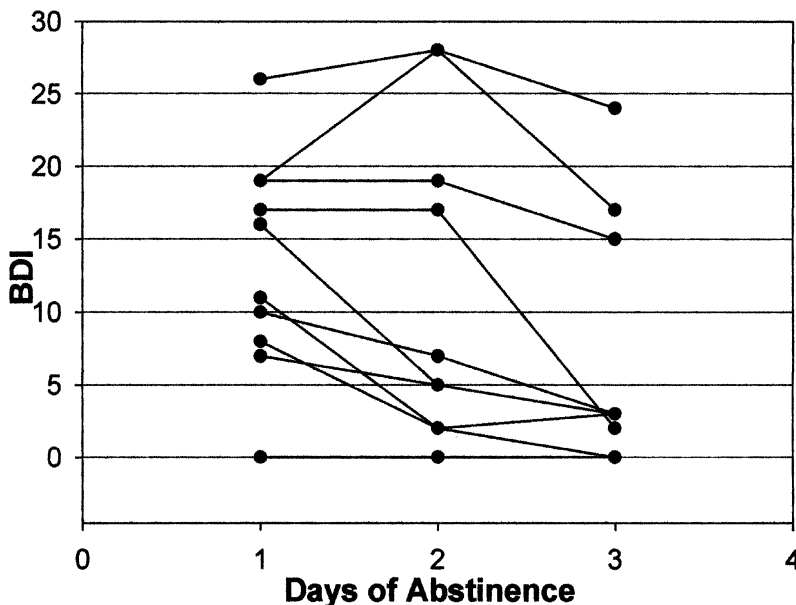


FIGURE 1. The early study entry group. Beck depression inventory scores over the first three days of abstinence.

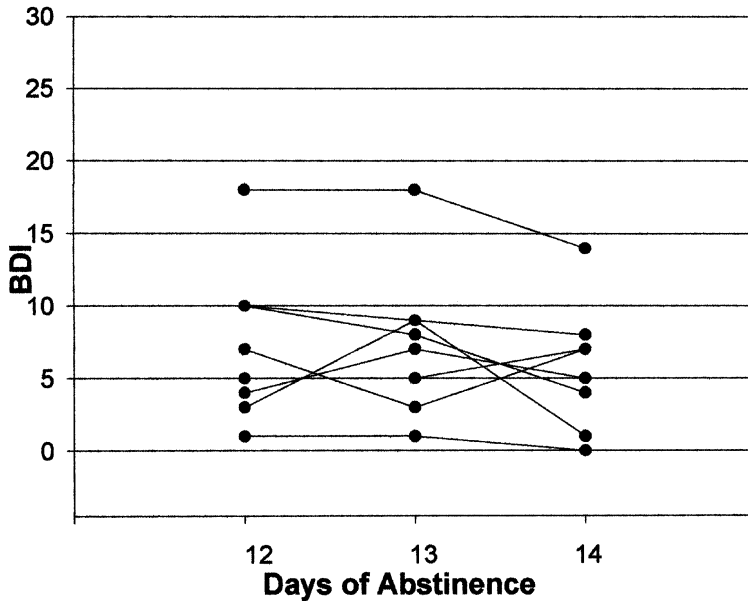


FIGURE 2. The late study entry group. Beck depression inventory scores following eleven days of monitored outpatient abstinence.

both Days 1 and 2. These items were anhedonia, irritability, and poor concentration ($p < .01$). Responses on two items showed strong trends when corrected for multiple comparisons (loss of energy and self-dislike, $p < .02$).

DISCUSSION

In the first three days following cessation of methamphetamine use, methamphetamine-dependent subjects reported a constellation of symptoms, the most prominent of which were anhedonia, irritability, and poor concentration. These symptoms generally contrast with those emphasized in the *DSM IV* criteria for amphetamine withdrawal, which include fatigue, unpleasant dreams, sleep disturbance, increased appetite, and psychomotor retardation or agitation. Excepting the “unpleasant dreams” criterion, these items are included in the BDI (questions 20, fatigue; 16, sleep disturbance; 18, appetite changes; 11, agitation; and 15 and 20, loss of

energy and tiredness or fatigue). Participants in this study did not endorse most items included in the DSM criteria for amphetamine withdrawal, although they had the opportunity to do so, suggesting that the symptoms were either prominent or not bothersome.

Participants in this study were more symptomatic than those examined previously in studies of cocaine dependence. Withdrawal symptoms were rated as nearly twice as severe, particularly during the first days of abstinence, as those reported following abstinence from chronic cocaine use.⁵ Nevertheless, participants in the early entry group reported substantial symptom reduction after several days of abstinence, and participants in the late entry group had generally mild symptoms throughout the study. This suggests that abstinence symptoms resolve spontaneously over time. Alternatively, participants in the late entry group used methamphetamine less frequently than did the participants in the early entry group, and less frequent use may be

associated with milder abstinence symptoms. A larger study in which all participants were evaluated daily after abstinence initiation would address this question.

Although the biology underlying the methamphetamine abstinence syndrome is unknown, methamphetamine has been shown to produce long-lasting reductions in neuronal expression of dopamine neuronal markers, including the dopamine transporter, tyrosine hydroxylase, and others.^{19–21} Cocaine, by contrast, appears to produce less severe neurotoxic effects than methamphetamine.²² The relationship between these neuroanatomical and neurophysiological changes and the self-reported symptoms is unclear. Particularly intriguing is the contrast between the rapid recovery of mood symptoms and the longer-lasting alterations in dopaminergic neuronal markers.

The item analysis indicated that abstinence symptoms presenting early in withdrawal paralleled those typically observed in major depression, which include depressed mood, anhedonia, change in appetite, sleep disturbance, psychomotor agitation or retardation, fatigue, guilt, poor concentration, and thoughts of death.² The symptoms reported by these methamphetamine-dependent volunteers were more limited, with depressed mood reported less frequently than apathy, suggesting that the methamphetamine abstinence syndrome may not mimic major depression entirely. Rather, anhedonia, lack of energy, irritability, and poor concentration characterize *apathy*, a syndrome commonly seen in the context of several neuropsychiatric disorders, such as Parkinson's disease, Huntington's disease, or progressive supranuclear palsy.²³ In each of these disorders, dysfunction of brain dopamine systems is prominent. Methamphetamine dependence is also characterized by a variety of abnormalities in brain dopamine systems,^{24–27} suggesting that the

methamphetamine abstinence syndrome may be characterized as a variant of the apathy syndrome. This has treatment implications because pharmacological treatments of apathy (dopaminergic agents) generally differ from the antidepressants used for the treatment of major depression.

Although the mean BDI score for the early abstinence group dropped into the minimal range by Day 3 of abstinence, data shown in Fig. 1 suggest that there may be three subgroups: those who do not experience methamphetamine abstinence syndrome, those in whom symptoms rapidly resolve, and those in whom symptoms persist beyond initial abstinence. This latter finding has potentially important implications for the development of treatments for methamphetamine dependence. Patients with prolonged abstinence symptoms may require targeted treatment that may differ from that for those without prolonged abstinence syndromes.

Even relatively transient mood disturbances may have important implications. Many methamphetamine-dependent subjects report using methamphetamine daily or almost daily (as in the early abstinence group, who used on twenty of the past thirty days). On days when they did not use methamphetamine, these subjects would be in the first days of abstinence much of the time. This may account in part for previous reports suggesting that depressive symptoms are more common among methamphetamine-dependent subjects than among subjects dependent on other drugs.²⁸

This study has several limitations. The sample size, particularly for the late group, was modest, so replication will be necessary to determine the stability of the findings. Although we were able to document abstinence during the outpatient phase of the study, it would be preferable to study all patients under the controlled conditions of an inpatient environment. Study participants self-selected entry into either early

abstinence group or the late abstinence group. Those entering the early group used methamphetamine more frequently and had greater distress than did those entering the late group. This may have confounded assessment of symptom severity, though even subjects in the early group reported substantial symptom resolution by Day 3. Our sample was limited to those methamphetamine-using volunteers who agreed to stop using methamphetamine and who did not have other psychiatric comorbidities. Participants with more severe abstinence symptoms or other psychiatric problems may not have volunteered for the study, thus biasing the sample toward subjects with less severe symptoms. The measure used (the BDI) though useful for characterizing particular depressive symptoms, collects only a limited range of information. Future studies should include a wider array of measures to characterize this syndrome more fully.

These findings provide empirical support for the clinical impression that

methamphetamine dependence is associated with an abstinence syndrome. There was substantial variability in the time-course of the syndrome, and, in spite of substantial methamphetamine use, not all subjects experienced abstinence symptoms. Most subjects reported reductions in symptoms within several days of abstinence initiation, which is a relatively brief period compared to the more prolonged time-course described in retrospective reports. Additional research will define optimal treatment approaches for this syndrome, whether pharmacological or behavioral.

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REFERENCES

1. Anglin MD, Burke C, Perrochet B, Stamper E, Dawud-Noursi S. History of the methamphetamine problem. *J Psychoactive Drugs*. 2000; 32:137-141.
2. *Diagnostic and Statistical Manual*. 4th ed. Washington, D.C.: American Psychiatric Association; 1994.
3. Gawin FH, Ellinwood EH Jr. Cocaine and other stimulants: actions, abuse, and treatment. *N Engl J Med*. 1988;318:1173-1182.
4. Cottier LB, Shillington AM, Compton WM, Mager D, Spitznagel EL. Subjective reports of withdrawal among cocaine users: recommendations for DSM-IV. *Drug Alcohol Depend*. 1993;33:97-104.
5. Weddington WW, Brown BS, Haertzen CA, et al. Changes in mood, craving, and sleep during short-term abstinence reported by male cocaine addicts: a controlled, residential study. *Arch Gen Psychiatry*. 1990;47:861-868.
6. Kampman KM, Volpicelli JR, McGinnis DE, et al. Reliability and validity of the Cocaine Selective Severity Assessment. *Addict Behav*. 1998; 23:449-461.
7. Coffey SF, Dansky BS, Carrigan MH, Brady KT. Acute and protracted cocaine abstinence in an outpatient population: a prospective study of mood, sleep and withdrawal symptoms. *Drug Alcohol Depend*. 2000;59:277-286.
8. Cantwell B, McBride AJ. Self-detoxification by amphetamine-dependent patients: a pilot study. *Drug Alcohol Depend*. 1998;49:157-163.
9. Churchill AC, Burgess PM, Peard J, Gill T. Measurement of the severity of amphetamine dependence. *Addiction*. 1993;88:1335-1340.
10. Srisurapanont M, Jarusuraisin N, Jittiwutikan J. Amphetamine withdrawal: I. reliability, validity and factor structure of a measure. *Aust N Z J Psychiatry*. 1999;33:89-93.
11. Srisurapanont M, Jarusuraisin N, Jittiwutikan J. Amphetamine withdrawal: II. a placebo-controlled, randomised, double-blind study of amineptine treatment. *Aust N Z J Psychiatry*. 1999; 33:94-98.

12. Beck AT, Ward CH, Mendelson J, Mock J, Erbaugh J. The Beck Depression Inventory. *Arch Gen Psychiatry*. 1968;4:561–571.
13. Spitzer R, Williams J, Gibbon M. *Structured Clinical Interview for DSM-IV (SCID)*. New York: New York State Psychiatric Institute, Biometrics Research; 1995.
14. McLellan AT, Luborsky L, Cacciola J, et al. Guide to the addiction severity index: background, administration, and field testing results. Pub No. Adm88. Washington, DC: U.S. Government Printing Office; 1988.
15. Nelson HE. *National Adult Reading Test (NART): Test Manual*. Windsor, UK: NFER Nelson; 1982.
16. Kalechstein AD, Newton TF, Green M. Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. *J Neuropsychiatry Clin Neurosci*. 2003;15:215–220.
17. Keppel G. *Design and Analysis: A Researcher's Handbook*. Englewood Cliffs, NJ: Prentice Hall; 1982.
18. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. New York: Oxford University Press; 1998.
19. Villemagne V, Yuan J, Wong DF, et al. Brain dopamine neurotoxicity in baboons treated with doses of methamphetamine comparable to those recreationally abused by humans: evidence from [11C]WIN-35,428 positron emission tomography studies and direct in vitro determinations. *J Neurosci*. 1998;18:419–427.
20. Melega WP, Lacan G, Harvey DC, Huang SC, Phelps ME. Dizocilpine and reduced body temperature do not prevent methamphetamine-induced neurotoxicity in the vervet monkey: [11C]WIN 35,428 – positron emission tomography studies. *Neurosci Lett*. 1998;258:17–20.
21. Ricaurte GA, Schuster CR, Seiden LS. Long-term effects of repeated methylamphetamine administration on dopamine and serotonin neurons in the rat brain: a regional study. *Brain Res*. 1980;193:153–163.
22. Little KY, Zhang L, Desmond T, et al. Striatal dopaminergic abnormalities in human cocaine users. *Am J Psychiatry*. 1999;156:238–245.
23. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci*. 1998;10:314–319.
24. Volkow ND, Chang L, Wang GJ, et al. Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *J Neurosci*. 2001;21:9414–9418.
25. McCann UD, Wong DF, Yokoi F, et al. Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C]WIN-35,428. *J Neurosci*. 1998;18:8417–8422.
26. Wilson JM, Kalasinsky KS, Levey AI, et al. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. *Nat Med*. 1996;2:699–703.
27. Melega WP, Raleigh MJ, Stout DB, et al. Recovery of striatal dopamine function after acute amphetamine- and methamphetamine-induced neurotoxicity in the vervet monkey. *Brain Res*. 1997;766:113–120.
28. Kalechstein AD, Newton TF, Longshore D, et al. Psychiatric comorbidity of methamphetamine dependence in a forensic sample. *J Neuropsychiatry Clin Neurosci*. 2000;12:480–484.