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Methadone Maintenance Improves Cognitive Performance After Two Months of Treatment

Staci A. Gruber
McLean Hospital and Harvard Medical School

Golfo K. Tzilos
McLean Hospital

Marisa M. Silveri
McLean Hospital and Harvard Medical School

Mark Pollack
Habit Management Institute and Massachusetts General Hospital

Perry F. Renshaw
McLean Hospital and Harvard Medical School

Marc J. Kaufman
McLean Hospital and Harvard Medical School

Deborah A. Yurgelun-Todd
McLean Hospital and Harvard Medical School

Methadone maintenance (MM) has received little scientific attention regarding neurocognitive effects. The present study examined cognitive function in 17 opiate-dependent subjects at baseline and after 2 months of MM treatment. Subjects demonstrated significant improvements from baseline on measures of verbal learning and memory, visuospatial memory, and psychomotor speed and reduced *frequency* of drug use (Addiction Severity Index) relative to baseline, although the total percentage of urine samples positive for additional illicit substances was slightly increased. No effect of illicit drug use was observed when the sample was stratified by urine toxicology results, suggesting that improvements in cognition were not associated with additional illicit drug use. Results suggest that opiate-dependent subjects exhibit significant improvement in cognitive function after MM treatment. Future investigations are needed to confirm these findings.

Keywords: methadone maintenance, opiate dependent, cognition

Derived from the opium poppy, heroin was originally developed as a substitute for morphine in an effort to deal with issues of addiction. It was soon recognized, however, that heroin is more addictive than morphine, which resulted in making the use of heroin illegal. Although the demand for heroin remains significantly lower than for other drugs such as cocaine, methamphetamine, and marijuana, the consequences of heroin abuse are such that its abuse poses a significant drug threat. Despite increasing knowledge of heroin's effects, rates of heroin abuse among adults have increased slightly after trending downward over the past few years. According to the Monitoring the Future data, use rates among college students declined each year from 2000 to 2002 before increasing slightly in 2003. Data indicate that rates of past year heroin use were higher among persons aged 18 to 25 (0.3%) than any other age group including those aged 12 to 17 (0.1%) and 26 or older (0.1%) (National Survey on Drug Use and Health, 2004). There has also been a fourfold increase in heroin use for individuals between the ages of 12 and 17 since the 1980s and 2003, and statistics indicate that 1.5% of all 10th and 12th graders have tried the drug at least once (National Institute on Drug Abuse [NIDA], 2004). Moreover, according to the 2003 National Household Survey on Drug Abuse, nearly four million American adults have tried heroin, with 314,000 reporting "annual" use during the previous year (National Household Survey on Drug Abuse, 2002; Substance Abuse and Mental Health Services Administration Office of Applied Studies, 2003). These data underscore the magnitude of the problem of heroin abuse in this country and suggest that research into pharmacologic treatment options for abuse is critical.

Deficits in memory, learning, and attention have been linked to chronic opiate use, although it remains unclear whether these deficits are permanent or reversible (Davis, Liddiard, & McMillan, 2002; Grant, Adams, Carlin, & Rennick, 1977). Although a variety of effective treatments are available for heroin addiction, methadone maintenance (MM) remains the most common and current treatment of choice for opiate addiction in the United States (Joseph,

Staci A. Gruber, Marisa M. Silveri, Perry F. Renshaw, Marc J. Kaufman, and Deborah A. Yurgelun-Todd, Cognitive Neuroimaging Laboratory, McLean Hospital, and Harvard Medical School; Golfo K. Tzilos, Cognitive Neuroimaging Laboratory, McLean Hospital; and Mark Pollock, Habit Management Institute and Massachusetts General Hospital.

Correspondence concerning this article should be addressed to Staci A. Gruber, Cognitive Neuroimaging Laboratory, Brain Imaging Center, McLean Hospital, 115 Mill Street, Belmont, MA 02478. E-mail: gruber@mclean.harvard.edu

Stancliff, & Langrod, 2000). Taken orally, this treatment relieves narcotic craving and suppresses opioid abstinence syndrome for 24 to 36 hours and is associated with reduced illicit drug use, reduced spread of hepatitis and HIV, and increased employment (NIDA, 2005; Galynker, Watras-Ganz, Miner, Rosenthal, Des Jarlais, & Richman, 2000; Kreek & Reisinger, 1997). Despite the fact that methadone has been used for more than 30 years, few studies to date have examined the effects of MM on neurocognitive functioning.

Opioid-induced cognitive deficits have been observed in rats treated chronically with morphine, as evidenced by impaired acquisition of reference memory in the radial arm maze (Spain & Newsom, 1991). Carlin (1986) has also demonstrated impairments in visuospatial and visuomotor function in human opiate users. Pakesch, Loimer, Grunberger, Pfersmann, Linzmayer, & Mayerhofer (1992) compared the performance of opiate abusers on a number of neuropsychological measures with that of healthy, nonusing controls and found that the opiate-dependent group was significantly more impaired regarding tasks of visual memory recall. Hill & Mikhael (1979) have reported that heroin abusers showed marked impairments on psychomotor tasks and measures of visuospatial memory. More recently, Ornstein, Iddon, Baldacchino, Sahakian, London, & Everitt (2000) found that chronic heroin use impairs performance on sequence generation tasks, spatial working memory, and visual pattern recognition memory. These findings are in contrast to early reports suggesting that opiate users and controls do not differ in frontal lobe function (i.e., abstract thinking; Bruhn & Maage, 1975) and verbal fluency (Rounsaville, Jones, Novelly, & Kleber, 1982). There is, however, a growing body of evidence that chronic opiate use is associated with significant impairment on several dimensions of cognitive functioning.

Some evidence suggests that alterations in neurocognitive functioning persist in patients on MM compared with healthy individuals (Carlin, 1986; Pakesch et al., 1992). Significant neurocognitive impairments in delayed recall of prose (episodic memory) have been observed in heroin-dependent outpatients as early as three hours after an acute dose of methadone (Curran, Kleckham, Bearn, Strang, & Wanigaratne, 2001). Impairment in performance on measures of psychomotor speed, working and long-term memory, decision making, and response inhibition has also been reported following several months of MM treatment (ranging from 5 to 60 months; Darke, Sims, McDonald, & Wickes, 2000; Mintzer & Stitzer, 2002).

Some early reports suggest that the performance of MM patients does not significantly differ from that of former heroin abusers or normal controls, however (Appel & Gordon, 1976). More recently, Mintzer & Stitzer (2002) reported that patients in long-term MM treatment (45 months) demonstrated similar time estimation and conceptual flexibility as control subjects. These findings suggest that some aspects of neurocognitive functioning, such as attention, may be unaffected by long-term MM treatment, whereas other domains such as learning and memory may be more susceptible to chronic methadone use.

To date, little is known about acute versus chronic effects of MM on the cognitive function of MM patients. The current study examined several areas of cognitive functioning in a group of opiate-dependent subjects at the beginning of a MM program and after two months of treatment. It was hypothesized that subjects receiving methadone would show neurocognitive improvement from baseline to two months of treatment, particularly in verbal and visuospatial memory. It was also hypothesized that neurocognitive improvement would be associated with reduced heroin and other drug use, with the largest improvement seen in subjects with little to no illicit drug use at the two-month follow-up.

Method

Subjects

Seventeen opiate-dependent subjects enrolled in an MM program were recruited through the Habit Management Institute (Boston, MA) to participate in a longitudinal study of neuropsychological performance. Subjects were included in this study if they were between the ages of 18 and 45, met DSM–IV criteria for opiate dependence, and were beginning MM treatment. All subjects received the Structured Clinical Interview for DSM–IV (SCID-P) to ensure that no additional Axis I pathology was present in any subject (aside from meeting DSM criteria for opiate dependence). Subjects were excluded if they were pregnant, had an organic mental disorder, seizure disorder, or central nervous system disease (e.g., multiple sclerosis or cerebral vascular incident), or if they had a history of head trauma or loss of consciousness. During the initial screening phase, subjects were informed that if they tested positive for pregnancy on the basis of the urine screen, they would not be able to participate in the study. This was confirmed at both visits to the neuroimaging center via a urine screen.

The ages of the subjects (11 men, 6 women) ranged from 25.8 to 60.1 years with a mean age of 41.2 ± 10.6 years. Average education of the cohort was 11.0 ± 1.9 years. MM patients were first evaluated an average of 15.7 ± 13.1 days after enrolling in the MM program, at which time their average methadone dose was 68.0 ± 21.7 mg/kg (see Table 1).

Procedure

All aspects of the research protocol were reviewed and approved by the Institutional Review Board of McLean Hospital. Written

Table 1
Demographic Features of Subjects on Methadone Maintenance (MM) Treatment

Demographic feature	MM subjects	
	Men (n = 11)	Women (n = 6)
Age (years ± *SD*)	44.0 (11.0)	36.2 (8.4)
Education (years ± *SD*)	10.6 (2.2)	11.8 (1.1)
Handedness (R, L)	9 R, 2 L	4 R, 2 L
Age of first heroin use (years ± *SD*)	21.0 (8.1)	21.0 (5.4)
Duration of heroin use (years ± *SD*)	23.2 (12.0)	15.2 (8.92)
Mean methadone dose (mg/kg ± *SD*)	70.0 (21.0)	64.0 (25.1)

informed consent was obtained from all subjects following a complete description of the study. Subjects completing the experimental protocol were compensated for their voluntary participation. Subjects were seen at approximately the same time of day for both their baseline and two-month visit, and all subjects received methadone in the morning, before their visit. In this way, although not timed to a precise hour, all subjects received their methadone on their regular schedule and completed their test batteries at approximately the same time of day for both their baseline and follow-up visits, which was generally midmorning.

Clinical assessment. Urine samples were collected from each subject (prior to testing) at the McLean Hospital Brain Imaging Center and screened for the presence of drug metabolites (Triage test, Biosite Diagnostics, Inc., San Diego, CA). Women were also tested for pregnancy using a commercially available urine test kit (QuPID One-Step Pregnancy, Stanbio Laboratory, Inc., San Antonio, TX). All subjects were tested for breath alcohol content (Alco Sensor III, Intoximeters Inc., St. Louis, MO). Subjects testing positive for pregnancy or alcohol were not permitted to participate in the study.

The Addiction Severity Index (ASI) was administered to the subjects on both visits by a trained research assistant in order to evaluate each subject's medical condition, employment/support status, drug use, alcohol use, illegal activity, family/social relations, and general psychiatric function (McLellan, Luborsky, Cacciola, Griffith, & O'Brien 1985). A composite score (ranging between 0.0 and 1.0) for each aspect of the ASI was calculated, with higher scores reflecting greater problem severity.

Neuropsychological assessment. Before neuropsychological testing, subjects were administered an abbreviated clinical interview to ensure patients met diagnostic criteria for opiate dependence, as well as a demographic questionnaire. Subjects were administered neuropsychological measures in two single sessions each lasting 60–90 minutes—the first at baseline and the second after two months of MM treatment. The battery of tests was administered by trained psychometricians and included measures sensitive to frontal/executive functioning, verbal learning and memory, visuospatial learning and memory, as well as attention and psychomotor speed (for review, see Gruber & Yurgelun-Todd, 2000). The tests included the Rey Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure Test (Rey-O), Digit Symbol Subtest from the Wechsler Adult Intelligence Scale—Revised, Controlled Oral Word Association Test (FAS), Trail Making A and B, and the Stroop Color Word Test (Lezak, Howieson, & Loring, 1988). In order to determine subjects' preference for using one hand as opposed to the other during common tasks such as writing, eating, or throwing a ball, all subjects also completed the Annett Handedness Scale (Annett, 1970). Alternate test forms were used at the two-month time point to avoid potential practice effects. It is of note that once enrolled, subjects were told that they would be evaluated at multiple time points; however, no specific discussion about repeat cognitive testing occurred, which prevented subjects from leaving their baseline neurocognitive evaluation and attempting to remember items for their two-month follow-up visit.

Data analyses. Repeated measures analyses of variance (α = .05) were conducted to examine the clinical functioning and neuropsychological performance of the MM subjects at baseline and after two months of treatment. Repeated measures analyses of covariance were also completed to examine the relationship between neuropsychological function and illicit drug use (ASI scores) and to co-vary the neuropsychological measures by urine toxicology results.

Results

Clinical Measures

As noted in Table 1, at baseline, subjects reported using heroin for 20.3 ± 11.3 years, with a mean age of first heroin use at 21.0 ± 7.0 years. As seen in Figure 1, a significant decrease in the frequency of drug use domain of the ASI was detected between baseline (0.30 ± 0.02) to the two-month time point (0.24 ± 0.02), $F(1, 16) = 6.16$, $p = .03$. No evidence of improvement on any other ASI domain was observed.

Toxicology results for the sample, listed in Table 2, indicate that although subjects reported significantly reduced frequency of illicit drug use (see Figure 1), the percentage of subjects whose urine tested positive for additional illicit substances increased from baseline to the two-month visit, most notably for cocaine, which increased from 12% at baseline to 35% at the two-month visit. These data indicate that despite a reduction in reported drug use frequency, illicit drug use in general increased over the two-month period, resulting in fewer clean (free of illicit drug) urine samples at the two-month visit.

Neuropsychological Performance

As illustrated in Table 3, significant improvements were evident on a number of neurocognitive measures. Improvement in verbal learning and memory was demonstrated in the RAVLT, a serial list learning test, which revealed a significant increase from baseline to two months in the number of words learned over five trials, $F(1, 16) = 11.2$, $p = .004$ (see Figure 2). Similar improvements in visuospatial memory, as measured by the Rey-O, were detected in the delayed (30 minutes) recall condition, $F(1, 16) = 5.5$, $p = .03$, with MM subjects recalling more figure details after a delay when tested at two months compared with baseline (see Figure 3). A trend toward improvement in the immediate recall condition was also observed, $F(1,$

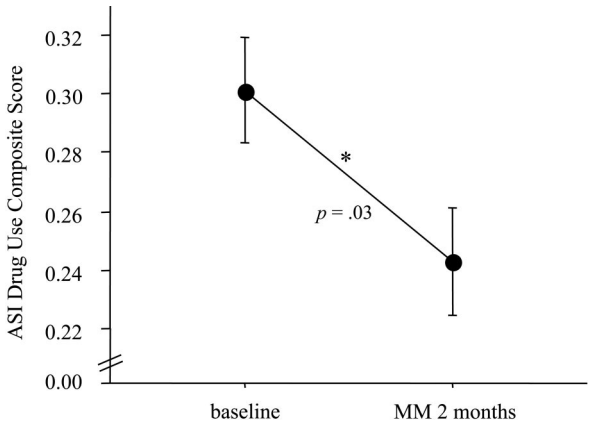

Figure 1. Addiction Severity Index (ASI) drug use frequency composite score. As measured by the ASI, frequency of use of additional illicit substances decreased between baseline and two months of methadone maintenance (MM) treatment, significant at $p = .03$.

Table 2
Urine Toxicology Results for Methadone Maintenance Subjects

Drug	Baseline	Two months methadone maintenance
Opiates	47%	47%
Cocaine	12%	35%
Amphetamine	0%	6%
Benzodiazepine	6%	18%
Barbiturate	12%	0%
Marijuana	6%	12%
Clean urines[a]	35%	24%

[a] Data represent percentages of positive urine tests at baseline or after two months of methadone maintenance ($n = 17$). Because urinalysis of methadone was unavailable on the test day, percentage of clean urines excludes methadone-positive samples.

16) = 3.62, $p = .08$, with MM subjects at the two-month visit recalling more details immediately (one minute) after the figure was removed than they did at their baseline visit. Subjects were able to reproduce a similar number of figure details in the copy condition at baseline and at two months of MM treatment, $F(1, 16) = 0.30$, $p = .59$, suggesting the improvements on the Rey-O were limited to conditions that included a memory component.

On the Wechsler Adult Intelligence Scale—Revised Digit Symbol Test, a test that requires subjects to transcribe digits to symbols as quickly as possible, subjects demonstrated a significant increase in correct responses after two months of MM, $F(1, 15) = 5.66$, $p = .03$. A trend toward improvement on the letter fluency (FAS) component of the Controlled Oral Word Association Test was also noted $F(1, 16) = 3.28$, $p = .09$, with subjects generating more words in each letter category after two months of MM treatment than at baseline. No significant differences were reported for the semantic component of the FAS, the Trail Making Test, parts A and B, or any subtest of the Stroop Color Word Test (see Table 3, Figures 4 and 5).

Discussion

In general, subjects on MM showed improvements in verbal and visuospatial encoding and recall as well as psychomotor speed after two months of treatment. Significant improvement was detected between baseline and two months of methadone treatment for the RAVLT, a serial list learning test that requires subjects to recall as many of 15 items as possible after the word list is read aloud. Verbal learning is defined as the total number of words recalled after 5 presentations, which was significantly improved after two months of methadone treatment. Improvement was also demonstrated on the Rey-O for the two conditions of the test that included a memory component. This test requires subjects to initially copy a complex figure (copy condition) using colored pens of their choice. Immediately after the removal of the stimulus figure, subjects are asked to recall as much of the figure as possible from memory (immediate recall condition). Finally, after a 30-minute delay, subjects are again asked to draw as much of the figure as possible from memory (delayed recall condition). Interestingly, after two months of treatment, subjects recalled significantly more information during the delayed recall

Table 3
Neuropsychological Test Performance at Baseline and After Two Months of Treatment

Test	Baseline (*M*, *SE*)	Two months (*M*, *SE*)	*F*	*p*
WAIS-R Verbal IQ Estimate		92.4 (11.3)		
Rey Auditory Verbal Learning				
Trial 1–5 (words recalled)	40.9 (2.73)	47.4 (2.56)*	11.20	.004
Rey-Osterrieth Complex Figure Test				
Copy condition	26.5 (1.50)	27.3 (1.28)	0.30	.59
Immediate condition	12.4 (1.51)	15.2 (1.48)	3.62	.08
Delay condition	11.0 (1.41)	14.03 (1.46)*	5.50	.03
Wechsler Adult Intelligence Scale—Revised (WAIS-R)				
Digit Symbol Test	42.9 (4.59)	49.2 (4.20)*	5.66	.03
Controlled Oral Word Association Test				
Letter fluency (FAS)	29.7 (2.70)	33.2 (2.95)	3.28	.09
Category fluency (animals)	18.4 (1.49)	18.0 (1.07)	0.26	.62
Trail Making				
Trail A (time)	42.4 (6.39)	34.5 (3.91)	2.98	.10
(Errors)	0.12 (0.08)	0.06 (0.06)	0.32	.58
Trail B (time)	103.0 (13.08)	100.8 (10.96)	0.05	.83
(Errors)	0.82 (0.26)	2.82 (1.74)	1.36	.26
Stroop Test				
Color naming (time)	76.0 (5.93)	69.4 (3.70)	1.81	.20
(Errors)	2.35 (0.62)	1.59 (0.42)	1.04	.32
Word reading (time)	57.7 (4.46)	54.7 (3.04)	0.62	.44
(Errors)	0.77 (0.41)	0.71 (0.36)	0.01	.92
Interference (time)	128.4 (7.03)	126.3 (7.95)	0.08	.78
(Errors)	4.06 (0.88)	2.94 (1.08)	0.85	.37

* Indicates significance change from baseline ($p < .05$). Data represented are means ($\pm$ *SE*s in parentheses).

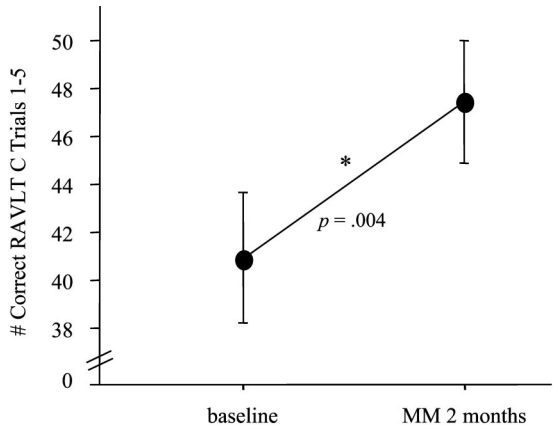

Figure 2. RAVLT C = Rey Auditory Verbal Learning Test—total number correct. A significant improvement in the total number of words recalled for Word Lists 1 through 5 was noted between baseline and two months of methadone maintenance (MM) treatment, significant at $p = .004$.

condition as compared to baseline. Further, a trend toward significance was detected in the immediate recall condition between baseline and two months of treatment. No improvement was observed between baseline and two months for the copy condition, underscoring the specificity of improvement in memory function. Subjects appear to perform the simple act of copying a figure similarly before and after methadone treatment, but they show significant improvement in recall function following the treatment period.

Improved performance was also noted for the Digit Symbol task, a test of psychomotor speed and working memory, which requires subjects to transcribe numbers to symbols as quickly as possible. Although the code for the transcription is directly above the response field, subjects must keep some of the information in mind to move quickly through the test. Subjects were able to complete more items after two months of treatment, indicating a benefit of treatment for the efficiency of generating psychomotor responses. Given that the task demand includes a working memory component, the improved results may be due to increased attentional capacity and memory load. Performance on the Controlled Oral Word Association (FAS) Test (which requires subjects to generate as many words as possible that begin with a specific letter within one minute) was also improved between baseline and two months of treatment, although this did not reach statistical significance. After two months of treatment, subjects were able to generate a greater number of appropriate responses to the letter cues.

A number of neurocognitive variables were not significantly changed between baseline and the two-month treatment period, suggesting that the improvements noted are related to specific domains. Performance on the Trail Making Test was not significantly different between the two time points for either Part A, a relatively pure measure of attention and psychomotor speed, or Part B, a measure of executive function that requires subjects to actively alternate mental set while completing the task, although they performed the task more quickly after two months of treatment. Similarly, no significant differences were detected for any of the conditions of the Stroop Color Word Test, which requires participants to name colors (color naming), read words (word reading), and finally report the color of words printed in an incongruent ink color as quickly as possible (interference). The interference condition requires that subjects actively inhibit an overlearned tendency (word reading) in favor of a less automatic tendency (color naming), which is also considered a measure of executive function. Taken together, these findings underscore the specificity of the improvements within tasks that involve a memory component, while tasks that measure executive functions or pure psychomotor speed appear to be relatively unchanged.

The total number of subjects with clean urine decreased slightly over the treatment period; however, as indicated by

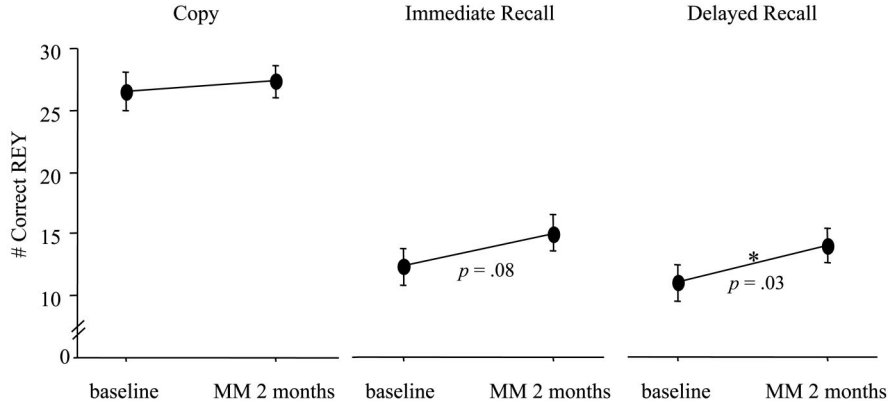

Figure 3. Rey-Osterreith Complex Figure Test (REY) performance. Despite similar performance on the copy condition, subjects demonstrated significantly improved performance on the delayed condition of the REY complex figure, significant at $p = .03$. A trend toward significance was also noted in the immediate recall condition of the test, underscoring the improvement in memory function, $p = .08$. MM = methadone maintenance.

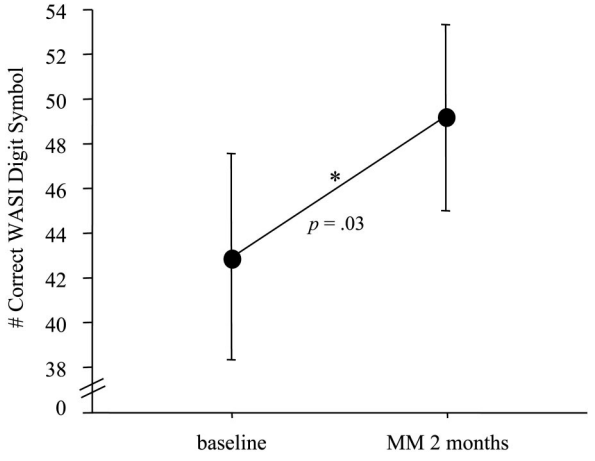

Figure 4. Digit Symbol Performance. A task that involves both psychomotor speed and working memory, performance on the Digit Symbol Test was significantly improved between baseline and two months of treatment, significant at $p = .03$.

the ASI, the frequency of illicit drug use was significantly reduced. Interestingly, the percentage of clean urine samples was moderately decreased after the two-month treatment period, and no effect of illicit drug use was observed when the sample was stratified by urine toxicology results, suggesting that improvements in cognitive function were not due to additional illicit drug use. Given the percentage of subjects who used cocaine increased from 12% at baseline to 35% at the two-month follow-up visit, separate analyses were completed after dividing the total sample into two groups: individuals who tested positive for cocaine at the two-month follow-up and individuals who tested negative for cocaine at the two-month follow-up. These analyses indicated that no significant effect of cocaine use was noted on any neuropsychological measure, however, subjects who were positive for cocaine metabolites after two months of treatment showed less improvement than those who did not use cocaine. For example, scores on the RAVLT improved for both groups between the baseline and two-month visit, but subjects who were positive for cocaine use showed less improvement than those who did not use cocaine (see Figure 6). It is possible that cocaine use by some of the subjects may have reduced the measurement of overall change in improved function associated with MM. A number of previous investigations have reported high rates of cocaine use in patients enrolled in MM programs (Condelli, Fairbank, Dennis, & Rachal, 1991; Kidorf & Stitzer, 1993). Studies that have focused on the pharmacologic interaction between the two drugs have shown that cocaine increases concentrations of endogenous opioids peptides in specific brain regions (Sivam, 1989) and has been shown to increase opioid-induced analgesia (Sierra et al., 1992). It is likely that the reinforcing effects of both cocaine and opiates are mediated via dopaminergic pathways, at least part of which are shared (Wise, 1988). Consistent with findings from opiate-cocaine interaction studies, Preston et al. reported that subjects who were maintained on methadone and taking cocaine demonstrated significantly increased subjective ratings of drug effects than those on cocaine alone (Preston et al., 1996). The rate of cocaine use in the current investigation is consistent with previous investigations and suggests that subjects may engage in higher cocaine use during the maintenance period in order to increase the effect of methadone, which is notably less intense, although longer lasting, than heroin. Given the reduction in narcotic craving and suppression of opioid abstinence syndrome associated with methadone and the increase of endogenous opioid peptides following cocaine use, the high rate of concomitant cocaine use in methadone-maintained subjects is not surprising.

Thus far, studies that have focused on the neurocognitive effects of chronic opiate and methadone use (Darke et al., 2000; Davis et al., 2002; Mintzer & Stitzer, 2002) have not evaluated the neuropsychological performance of MM patients longitudinally. The unique within-subjects design of the current study allowed for comparisons between the cognitive function of opiate-dependent subjects at baseline and after two months of MM treatment. A recent cross-sectional study comparing the neuropsychological performance of former opiate-dependent subjects enrolled in a drug rehabilitation center (drug free), opiate-dependent subjects enrolled in an MM program, and healthy controls reported few differences between the three groups (Davis et al., 2002). The most significant difference identified was that MM patients performed more poorly on a measure of verbal fluency than did the controls and drug-free opiate-dependent patients. Interestingly, the MM patients in the current study tended to improve in verbal fluency after two months of treatment, suggesting that the impairment noted by Davis et al. may be reversible. Subjects in the current study were also on a higher average daily dose of methadone (70 mg) compared to the Davis et al. cohort (32.4 mg).

The findings of the present study are constrained by the moderate sample size ($n = 17$) and should therefore be considered preliminary. The data should also be interpreted with caution given the high rate of polydrug use (and history

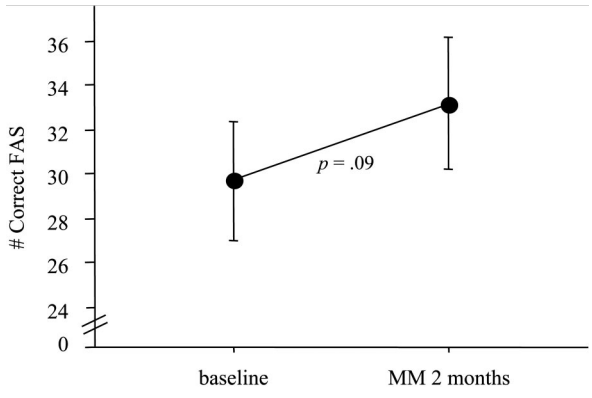

Figure 5. Verbal Fluency Performance. Improvement in the total number of words generated to a cue letter was detected between baseline and two months of treatment, which trended toward significance, $p = .09$. FAS = Controlled Oral Word Association Test, letter fluency component; MM = methadone maintenance.

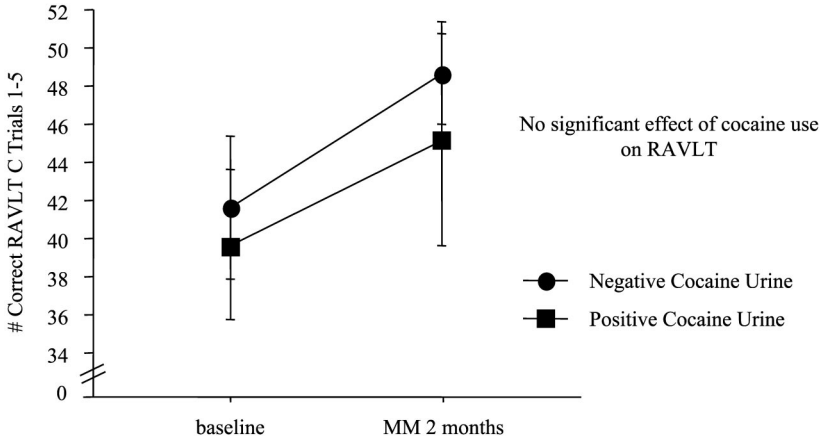

Figure 6. Rey Auditory Verbal Learning Test—total number correct: cocaine users versus non-cocaine users. No significant effect of cocaine use in the total number of words recalled for Word Lists 1 through 5 was noted between baseline and two months of methadone maintenance (MM) treatment. Although both negative and positive cocaine users improved between baseline and two months, non-cocaine users showed more improvement.

of polydrug use) in the subject pool. Further, it is important to note that there was no comparison treatment arm in this study, making it difficult to ascertain whether the improvement in the patients' cognitive function after two months of MM treatment was due to methadone itself, or merely the effect of being in a treatment program. It is of note, however, that the estimated verbal IQ of the sample was 92.4 $\pm$ 11.3, which is well within the average range, suggesting that the profile demonstrated within the study sample is not the result of poor overall cognitive function.

We cannot rule out the possibility that some subjects experienced slight sedation during the baseline visit given their recent exposure to methadone, as some early studies have reported this in animals during the initial phases of treatment (Crowley, Hydinger, Stynes, & Feiger, 1975), although no subjects reported this at either testing session. A review of the neurocognitive scores suggests that the improvements shown in the current study are not the result of a wearing off of sedative effects. For example, the word reading subtest of the Stroop Color Word Test requires only that subjects read words printed in black ink as quickly as possible. At the baseline visits, subjects took an average of 57.7 seconds to complete the task, which is at the high end of normal limits. Although some improvement was detected at the two-month follow-up visit, (average time to complete was 54.7 seconds), no significant difference between the time points was demonstrated. If subjects were experiencing enough sedation at baseline that abated by their two-month visit, we would expect that subjects would have shown more significant differences between the two time points on tasks sensitive to attention and psychomotor speed. It is also of note that subjects' performance on the Trail Making A Test, a measure of psychomotor speed, vigilance and attention, was well within normal limits at both visits and no significant difference between the time points was detected. The issue of possible sedation is, however, an important point for future longitudinal studies.

In conclusion, MM improved cognitive performance, particularly on tests of learning and memory. These improvements do not appear to be the result of practice effects, as alternate test forms were used at each testing period. Furthermore, the improvements remained significant even after co-varying for illicit drug use. Future longitudinal studies seeking to replicate the findings of the current study should include a group of opiate-dependent subjects enrolled in a non-MM treatment program, as well as a group of healthy control subjects, in order to better characterize the degree of neuropsychological improvement in MM patients. Given recent findings demonstrating a relationship between methadone dose and neuropsychological performance (Curran et al., 2001; Hepner, Homewood, & Taylor, 2002) in which higher doses lead to greater impairment, future studies should also take into account the effects of dose and tolerance effects when assessing the neuropsychological performance of MM patients. Findings from the current investigation may be used to plan treatment strategies that are enhanced by improved memory function.

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