Neuropsychological functioning in buprenorphine maintained patients versus abstinent heroin abusers on naltrexone hydrochloride therapy

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Rationale  Methadone and buprenorphine are among the most widely employed pharmacological treatments currently available for opioid addiction. Cognitive effects of buprenorphine in abstinent heroin abusers are nevertheless far from being understood.

Methods  Neuropsychological performance of 18 buprenorphine-maintained patients (BMP) was evaluated relative to that of 32 currently abstinent heroin abusers on naltrexone hydrochloride therapy (FHAN), and 34 non-drug dependent controls. The three groups were demographically balanced. Clinical groups reported histories of similar patterns of drug use and had increased periods of abstinence from any illicit substance use including heroin.

Results  The BMP group performed poorer than controls on the RAVLT (encoding and delayed recall of verbal information), CTT (conceptual flexibility, executive functions) and the RBANS figure copy (visual perception) and delayed recall of visual information. There were no significant differences in any of the cognitive measures between the BMP and FHAN groups or between the FHAN group and controls. Furthermore, the non-differing percentage of abnormal cases between the two patient groups led us to infer that treatment with either BPM or FHAN is not accompanied by qualitative differences in the cognitive profiles of these patients.

Conclusion  Overall, results suggest that treatment with naltrexone in abstinent heroin abusers may result in less impairment of cognitive functions compared to treatment with buprenorphine. These findings are relevant for improved prognosis and treatment strategies in opioid dependence. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS— neuropsychological; buprenorphine; naltrexone; maintenance

INTRODUCTION

Opioid abuse constitutes a significant public health problem, with over nine million people estimated to abuse heroin worldwide (United Nations Office on Drugs and Crime World Drug Report, 2004). Besides, several studies indicate that chronic opioid dependence is associated with impairments in cognitive performance that might affect daily functioning. In particular, long-term opioid use has been associated with cognitive deficits, often involving frontal lobe functions. Such deficits extend to several executive and emotional processes (Gruber et al., 2007; Pulvirenti and Diana, 2001; Verdejo-García et al., 2006). These impairments may contribute to the relapsing nature of addictive disorder.

Methadone and buprenorphine are among the most widely employed pharmacological treatments currently available for opioid addiction (European Monitoring Centre for Drugs and Drug Addiction, 2006). However, a number of studies indicate that methadone maintenance treatment may itself be linked to impairments in several cognitive functions, possibly extending impairments attributable to long-term opioid abuse (Curran et al., 2001; Davis et al., 2005; Mintzer et al., 2005; Prosser et al., 2006; Verdejo et al., 2005). By contrast, beneficial effects on cognition compared to baseline after 2-months methadone maintenance treatment have been reported recently (Gruber et al. 2006). In any case, since there is sufficient evidence in the literature that opioid-induced cognitive impairment of addicted patients may
contribute to treatment success, (Gossop et al., 2003; Teichner et al., 2002) it is important to assess pharmacological treatment options alternative to methadone with respect to neuropsychological functioning.

While methadone is a pure and unselective opioid agonist, buprenorphine is currently classified as a mixed agent (i.e., partial μ-opioid receptor agonist and κ-receptor antagonist with a long duration of action). In addition, κ receptors are located in cortical areas, raising the possibility that pharmacological manipulation of this receptor may affect cellular mechanisms crucial for cognitive function in opioid dependent individuals. Thus, pharmacological antagonism of κ-opioid receptors obtained with buprenorphine could potentially modulate cognitive functions. Furthermore, buprenorphine treatment has been shown to reduce κ-receptor availability in cortical brain areas crucial for cognitive functions (Greenwald et al., 2003; Zubieta et al., 2000).

As a partial μ-opioid receptor agonist, buprenorphine may be associated with reduced sedation and impairment of psychomotor and cognitive performance (Boothby and Doering, 2007). In line with this, escalation of buprenorphine dose exhibits no major influence on a wide range of complex cognitive functions in opioid-dependent subjects (Boothby and Doering, 2007). Furthermore, injection of methadonemaintained subjects with buprenorphine up to 8 mg did not impair their cognitive functioning (Strain et al., 1995).

Cognitive effects of buprenorphine in abstinent heroin abusers is nevertheless far from being understood. Available studies have focused mainly on neuropsychological comparison of buprenorphine maintenance treatment (BM) versus methadone maintenance treatment (MM) in opioid-dependent individuals. Several studies have demonstrated improved cognitive performance in patients maintained on buprenorphine compared to methadone (Rapeli et al., 2007; Soyka et al., 2001) and improved decision making ability (Pirastu et al., 2006). However, in this latter study, evaluation of patients 12 months after opioid substitution treatment, showed that both BM and MM patients performed inferior to controls in visual short-term memory. Moreover, Soyka et al. (2005) did not find significant differences in cognitive performance of opioid-dependent patients randomly assigned to either BM or MM with only a tendency towards improved psychomotor performance of BM patients.

Naltrexone, a fairly long-acting opioid antagonist, was approved by the US Food and Drug Administration for the treatment of opioid dependence in 1984. Naltrexone is not addictive, and treats opioid addiction at the receptor level instead of only withdrawing or substituting opioid agonists. It is a relatively safe drug but some controversy exists in the literature regarding its clinical effectiveness in the treatment of opioid addiction (Minozzi et al., 2006). To date no data is available in the literature regarding the effects of naltrexone on cognition in human subjects. However, when naltrexone (2 mg/kg, ip) was administered to young and aged rats prior to testing to assess possible improvements in aged-related cognitive impairments, it attenuated impairments in cognitive function in the extradimensional shift discrimination learning task (EDS) for aged animals, but did not alter any task performance in the younger group (Rodefer and Ngugen, 2008).

To our knowledge, no studies have examined neuropsychological functioning during maintenance treatment with the opioid agonist buprenorphine (Subutex®) and treatment with naltrexone hydrochloride (Nalorex®). Thus, the aim of the present study was to compare the neuropsychological performance of a group of buprenorphine-maintained patients (BMP) relative to a group of currently abstinent heroin abusers (FHAN) on naltrexone hydrochloride therapy, and a group of non-drug dependent controls (C). We focused on a broad range of cognitive functions shown previously to be influenced by opioid abuse and/or dependence and buprenorphine maintenance treatment.

MATERIALS AND METHODS
Participants
We recruited 50 patients from two separate drug treatment programs (18 from the OKANA detoxification Unit in Patras, Greece and 32 from the detoxification and psychosocial substance rehabilitation program offered at the “Merimna Life Care Unit” in Athens, Greece). We also recruited 34 age, sex, education, and intelligence matched healthy controls from the community. All participants in the two clinical groups were diagnosed as persons with opioid dependence (DSM-IV-TR criteria, American Psychiatric Association, 2000) and self-reported consumption of heroin as drug of choice in the past year. Furthermore, they were required to be stably participating in either a buprenorphine-maintenance program (BMP) (range: 18–28 weeks of maintenance), or should be former (abstinent) heroin abusers (FHAN) on naltrexone hydrochloride therapy for at least...
3 months or non-drug dependent (C). The FHAN group was participating in an opioid detoxification rehabilitation program after having initially undergone an ultra rapid opioid detoxification procedure. Patients in this outpatient program received naltrexone (50 mg/day) and psychosocial support for a minimum period of 12 months. Participants in both clinical groups provided routine urine samples as part of their program requirements and before the neuropsychological testing session. Urinary toxicology screening further confirmed that no other illicit substances had been used by participants following the detoxification procedure for the FHAN group and during the course of buprenorphine treatment for the BMP group.

All patients were also clinically evaluated for psychiatric status according to DSM-IV-TR (American Psychiatric Association, 2000) criteria using SCID axis I, II, and by a specialist neurologist in order to exclude neurological disorders. Exclusion criteria included: organic CNS pathology-neurological disorders, HIV/HCV infection, major psychopathology, head trauma resulting in loss of consciousness for longer than 5-min, dementia, mental retardation, and current therapy with medications or medical conditions known to affect cognition, other illicit substance dependencies including alcohol for the past 6 months prior to inclusion in the maintenance therapy (excluding opioids), non-native speakers of the Greek language and ages 20–45. All participants provided informed consent to participate in the study, and permission to conduct the study was obtained by the local ethics committee University of Patras Medical School, (see Table 1 for demographic and clinical characteristics of the participants).

**Neuropsychological measurements**

The neuropsychological test battery consisted of a broad range of cognitive tasks shown in previous studies (Gruber et al., 2007; Pirastu et al., 2006; Pulvirenti and Diana, 2001; Rapeli et al., 2007; Soyka et al., 2001; Verdejo-Garcia et al., 2006) to be influenced by opioid abuse and buprenorphine treatment. All neuropsychological tests were adapted for the Greek population and administered using standard procedures in single sessions (see Table 2).

### Table 1. Demographic and clinical characteristics and self-reported drug use history (lifetime duration (years) and percentage used in last 6 months) mean (SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>BMP</th>
<th>FHAN</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>83.3</td>
<td>81.3</td>
<td>79.4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.50 (5.52)</td>
<td>36.44 (4.98)</td>
<td>35.71 (4.46)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.00 (2.42)</td>
<td>11.19 (2.08)</td>
<td>11.50 (1.83)</td>
</tr>
<tr>
<td>Estimated intelligence level</td>
<td>94.25 (10.32)</td>
<td>96.54 (9.78)</td>
<td>97.86 (11.24)</td>
</tr>
<tr>
<td>IQ(^a)</td>
<td>6.78 (2.60)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Buprenorphine (mg/day)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Naltrexone dose (mg/day)</td>
<td>50.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Days of abstinence from Heroin(^b)</td>
<td>71.72 (53.21)</td>
<td>167.81 (47.72)</td>
<td>—</td>
</tr>
<tr>
<td>Drug use history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lifetime duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>12.82 (7.64)</td>
<td>11.43 (4.60)</td>
<td>—</td>
</tr>
<tr>
<td>Cannabis(^b)</td>
<td>12.83 (8.06)</td>
<td>15.85 (5.58)</td>
<td>—</td>
</tr>
<tr>
<td>Cocaine</td>
<td>9.86 (5.84)</td>
<td>10.54 (4.95)</td>
<td>—</td>
</tr>
<tr>
<td>Alcohol</td>
<td>12.57 (8.06)</td>
<td>11.92 (5.60)</td>
<td>12.86 (7.42)</td>
</tr>
<tr>
<td>Nicotine(^b)</td>
<td>16.35 (9.75)</td>
<td>13.86 (5.90)</td>
<td>14.74 (6.58)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>4.40 (4.26)</td>
<td>3.95 (3.68)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Percentage used in last 6 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>100</td>
<td>100</td>
<td>—</td>
</tr>
<tr>
<td>Cannabis(^b)</td>
<td>48</td>
<td>65</td>
<td>—</td>
</tr>
<tr>
<td>Cocaine</td>
<td>42</td>
<td>44</td>
<td>—</td>
</tr>
<tr>
<td>Alcohol</td>
<td>38</td>
<td>40</td>
<td>42</td>
</tr>
<tr>
<td>Nicotine(^b)</td>
<td>72</td>
<td>76</td>
<td>55</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>5</td>
<td>8</td>
<td>—</td>
</tr>
</tbody>
</table>

\(a\)Intelligence level was estimated by administering the vocabulary and matrix reasoning subscales of the Wechsler abbreviated scale of intelligence (WASI), Greek adapted version (Messinis et al., 2009). The vocabulary subscale is a good measure of crystallized intelligence, correlates well with general intellectual ability and is relatively insensitive to cortical insults (i.e., a good measure of premorbid intellectual ability). The matrix reasoning subscale is a measure of non-verbal fluid reasoning and correlates well with general intellectual ability. These two subscales yield an estimated full-scale IQ

\(b\)Significant difference among groups on that variable (\(p \leq .05\), all other comparisons were not significantly different.

Table 2. Neuropsychological test battery arranged by cognitive function assessed

<table>
<thead>
<tr>
<th>Cognitive function/s</th>
<th>Test used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal fluency/language</td>
<td>Boston Naming Test 15-item (Tsolaki et al., 2003)</td>
</tr>
<tr>
<td></td>
<td>Verbal Fluency Test: phonemic and semantic fluency (Kosmidis et al., 2004)</td>
</tr>
<tr>
<td>Verbal learning/memory</td>
<td>Rey Auditory Verbal Learning Test (Messinis et al., 2007a)</td>
</tr>
<tr>
<td>Visual leaning / memory</td>
<td>Repeatable Battery for the Assessment of Neuropsychological Status (complex figure task) (Messinis et al., 2008)</td>
</tr>
<tr>
<td>Psychomotor speed /attention</td>
<td>Color Trails Test part 1 (Messinis et al., in press)</td>
</tr>
<tr>
<td></td>
<td>Symbol Digits Modalities Test (Argirokastriou et al., 2005)</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>Color Trails Test part 2(Messinis et al., in press)</td>
</tr>
<tr>
<td>Severity of depression</td>
<td>Beck Depression Inventory –Fast Screen (Beck et al., 2000)</td>
</tr>
<tr>
<td>Selective–Sustained attention</td>
<td>Ruff 2 &amp; 7 Selective Attention Test (Messinis et al. 2007b)</td>
</tr>
</tbody>
</table>

Note: Normative data were taken from the sources indicated by reference.

Statistical analysis

The normality assumption of our data was initially investigated using the Kolmogorov–Smirnov test. One-way analysis of variance (ANOVA) was used to explore group differences in age, years of education, intelligence level, neuropsychological variables, and clinical characteristics. Group differences regarding sex and proportion of impairments in the various neuropsychological measures were examined using $X^2$ analysis. In order to investigate the equality of means we used independent samples $t$-tests for normally distributed variables, and the Mann-Whitney $U$ test for variables not normally distributed. In cases where statistically significant differences were found between the variances of groups, the $t$-test of unequal variances was used and the degree of freedom was estimated using the Welch–Satterthwaite approximation. We also calculated the proportion of impairment on individual neuropsychological measures using 2 standard deviations below the control group mean as criterion for impairment. We established an alpha level $\leq 0.05$ for statistical significance in all comparisons and all analyses were conducted using the SPSS 15.0 software. Bonferroni adjustment was used to avoid multiple post hoc test effects.

RESULTS

Initial analyses of confounding variables did not reveal significant differences between the three groups regarding age ($F_{2,81} = 5.777; p = .787$), years of education ($F_{2,81} = 1.644; p = .678$), sex ($\chi^2 = .120; p = .942$), or intelligence level ($F_{2,81} = 2.894; p = .852$). However, we found a significant difference in duration (days) of abstinence from heroin between the BMP and FHAN groups ($z = -4.984, p < .001$) with the nalorex group having abstained for a longer period. Only BMP and FHAN users reported use of benzodiazepines, heroin, cannabis, or cocaine. There were no significant differences among groups in reported lifetime duration of cocaine ($p = .658$), alcohol ($p = .592$), or benzodiazepine ($p = .847$) use. However, we noted a significant difference in reported lifetime duration of cannabis use, such that FHAN patients reported a significantly higher duration than BMP patients ($t = -2.932, p = .014$). Furthermore, we found a group effect on reported duration of nicotine use ($F_{2,81} = 1.562; p = .027$), with BMP patients reporting the longest duration. Although control participants reported longer duration of nicotine use than the FHAN group, post hoc comparisons revealed a difference only between the BMP and FHAN groups ($p = .012$).

Regarding the percentage of substances used by participants in the last 6 months prior to entering one of the maintenance programs or the controls, we found a significant difference in reported use of cannabis and nicotine, such that a significantly greater percentage of FHAN than BMP participants reported use of cannabis ($\chi^2 = 11.30; p = .042$), and a significantly greater percentage of FHAN patients than controls used nicotine ($\chi^2 = 16.30; p = .038$).

Further analyses of the neuropsychological data showed a group effect on Trial 1 of the RAVLT ($F_{2,81} = 6.230; p = .003$). Post hoc comparisons revealed a significant difference only between the BMP group and controls ($p = .017$) with the BMP group demonstrating inferior performance in initial encoding of verbally presented information. Furthermore, we found a significant group effect for the delayed recall trial of the RAVLT ($F_{2,81} = 1.659; p = .004$), with post hoc comparisons indicating a difference between the BMP group and controls ($p = .041$), with the BMP group demonstrating inferior performance in recalling previously verbally learned information. We found a significant main effect for the CTT 2 ($F_{2,81} = .426; p = .045$). Post hoc comparisons revealed a significant difference only between the BMP group and controls ($p = .036$), indicating possible reduced visual scanning ability, conceptual flexibility, and information processing speed in the BPM patients. A significant main effect was also noted on the RBANS figure copy ($F_{2,81} = 4.524; p = .014$) and RBANS delayed figure recall visual memory task ($F_{2,81} = 3.501$;
the RBANS figure copy (\( \chi^2 = 5.034; p = .025 \)), and RBANS delayed figure recall (\( \chi^2 = 3.877; p = .049 \)) and SDMT task (\( \chi^2 = 3.877; p = .049 \)), between the BMP and control group, with the BMP group demonstrating a higher proportion of impaired individuals in all three of the above cognitive measures compared to the controls. The BMP and FHAN groups did not differ significantly in the proportion of impaired individuals on any of the neuropsychological measures.

**DISCUSSION**

The present results suggest that the BMP group performed poorer than controls on several cognitive tasks. However, the non-differing percentage of abnormal cases between the two patient groups led us to infer that treatment with either BPM or FHAN is not accompanied by qualitative differences in the cognitive profiles of subjects. Also overall means of neuropsychological test performance did not differ between the two clinical groups, as indicated by post hoc comparisons. Further, analytic quantitative comparisons revealed that only the BMP group had statistically significant inferior performance compared to controls on select tests loading primarily on executive functions. Even when a similar proportion

\[ p = .035 \]. Post hoc comparisons revealed differences only between the BMP and control group in both the copy (\( p = .047 \)) and delayed recall tasks (\( p = .044 \)) (see Table 3). No significant post hoc comparison in any neuropsychological measure occurred between the BMP and FHAN groups, or between the FHAN group and controls.

There were several different patterns in the proportion of impairments seen across the groups (see Table 4). More specifically, we found a significant difference in the proportion of impaired individuals on the RBANS figure copy (\( \chi^2 = 5.034; p = .025 \)), and RBANS delayed figure recall (\( \chi^2 = 3.877; p = .049 \)) and SDMT task (\( \chi^2 = 3.877; p = .049 \)), between the BMP and control group, with the BMP group demonstrating a higher proportion of impaired individuals in all three of the above cognitive measures compared to the controls. The BMP and FHAN groups did not differ significantly in the proportion of impaired individuals on any of the neuropsychological measures.
of BMP compared to FHAN subjects were judged to be impaired, their impairments were more profound when present. Interestingly, both groups of opioid-dependent subjects performed similar to demographically and intelligence matched healthy drug-free subjects on tests of verbal abilities, as well as sustained and selective attention. Some studies have described partial recovery of cognitive deficits during abstinence. Opioid addicts exhibit less severe PFC cognitive deficits during abstinence than during drug consumption (Gruber et al., 2007; Soyka et al., 2008). In one study, addicts under stable treatment with either buprenorphine or methadone for 8–10 weeks both exhibited improvement in concentration skills and executive functions but their performance was still inferior to that of controls, indicating residual cognitive impairment in both groups (Soyka et al., 2008). Consistently, our results suggest that this functional recovery may be incomplete since we observed persistent deficient performances in former heroin users mainly on tests associated with frontal lobe functioning. Set-shifting ability closely dependent on inhibition is essential for successful performance on the Color Trails Test part 2 (CTT2). The dorsal anterior cingulate cortex (dACC) linked to response inhibition in humans has been shown to be biochemically and physiologically abnormal in long-term opioid-dependent individuals maintained on either methadone or buprenorphine (Yücel et al., 2007).

Significant cognitive deficits were found on measures of perceptual motor speed that also required cognitive flexibility and a task-switching component (CTT 2) and the SDMT on which performance is favored by implementation of effective strategies, but not on tasks that tested more restricted visuo-motor speed and attention functions (CTT 1) or even sustained and selective attention in the face of distraction (Ruff 2 and 7). Notably, analysis revealed persistent impairments; however, only the BMP group performed significantly poorer than controls on a test of visuo-spatial perception/visual memory (RBANS Complex figure task) indicating that visual representations of complex objects within memory are altered in opioid abusers even after relatively long periods of abstinence. The BMP group appeared to be less efficient than controls in encoding verbal information during the immediate/or working memory task. Effective retrieval of verbal and visual information from memory storage requires executive processes and was also shown to be impaired in a relatively high proportion of the clinical groups. Moreover, the BMP group had significantly inferior performance relative to controls on delayed verbal memory. Semantic fluency which requires organizational strategies for the production of as many words as possible belonging to certain categories was also impaired in as high as one tenth of patients in both groups, although a quantitative comparison yielded no significant differences across groups. Furthermore, we assume a deficit of visuo-constructive ability in patients more pronounced in those maintained on buprenorphine as judged by their performance on the RBANS Figure Copy Test.

Whether neuropsychological deficits observed in our patients are the product of chronic drug use or rather pre-existed and have contributed to development of drug dependence is still a matter of debate. Patient groups in our study were however matched with regard to premorbid intelligence and education. Furthermore, subjects with major comorbid psychopathology were excluded and scores on the degree of emotional affect as measured by the BDI-FS did not differ across groups. Nevertheless, it is still possible, that premorbid personality features or cognitive deficits might vary across groups and have influenced neuropsychological findings.

No differences in co-abused substances (alcohol, sedatives, stimulants, hallucinogens, opioids) were observed between patient groups, except that the FHAN group reported a higher percentage of relatively recent and also a longer lifetime duration of cannabis use, possibly related to subtle cognitive deficits as reported by our group recently (Messinis et al., 2006). This difference in cannabis consumption between the two clinical groups, however, strengthens the notion that naltrexone therapy could have been beneficial in terms of cognitive deficits in these patients attributable to cannabis as well.

Duration of treatment directly associated with period of abstinence from opioids may have accounted for the discrepancies in the degree of cognitive deficits observed in some of the cognitive domains. The BMP group had abstained for a significantly shorter period than the FHAN patients and one could claim that residual effects of heroin use on cognition were not balanced across the patient groups. The periods of abstinence confirmed by urine tests, guaranteed however, that heroin was sufficiently “washed out” in both clinical groups. Thus, neuropsychological deficits could not be attributed to acute intoxication. Undoubtedly, the relatively better cognitive performance in the FHAN group could bear other explanations as well.

Possible recovery of cognitive functioning during the maintenance period may be achieved not only through
pharmacological treatment, but also through psycho-social integration and psychological support. Thus, the higher cognitive performance in the FHAN group could be due to these additional therapeutic approaches that patients in this group were provided with. On the other hand, factors associated with the initial motivation of patients to participate in each of the addiction treatments may be of relevance, since naltrexone or buprenorphine was patients’ preferred method of treatment. Furthermore, naltrexone’s full opioid antagonist effect could be beneficial on cognitive functioning as has been shown in experimental animal studies (Rodefer and Ngugen, 2008). Interestingly, naloxone, another opioid antagonist, has been reported to enhance synaptic plasticity in the hippocampus of aged-rats (Zhao et al., 2004).

Overall, results suggest that treatment with naltrexone in abstinent heroin abusers may result in less impairment of cognitive functions compared to treatment with buprenorphine. Whether buprenorphine has an impact on cognitive functioning beyond that associated with chronic opioid abuse; however, requires further clarification. In order to delineate further the time course and enduring features of neuropsychological deficits among polydrug users, and to more clearly establish the relationship of opioid use to such impairment, future studies should include former opioid abusers participating in drug-free programs as controls to subjects undergoing substitution treatments and assess neuropsychological functions longitudinally. In any case, clinically it is important to acknowledge these findings, since they might be relevant to prognosis and treatment strategies in opioid dependent individuals and affect their social function and rehabilitation.

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