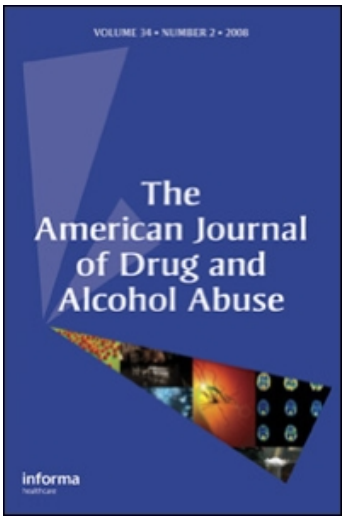

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Sabine Loeber [a]; Anja Kniest [a]; Alexander Diehl [a]; Karl Mann [a]; Bernhard Croissant [b]
[a] Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Mannheim, University of Heidelberg, Germany [b] Department of Psychiatry, Psychotherapy and Psychosomatics, Teaching Hospital Sigmaringen, University of Tuebingen, Germany

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Neuropsychological Functioning of Opiate-Dependent Patients: A Nonrandomized Comparison of Patients Preferring either Buprenorphine or Methadone Maintenance Treatment

Sabine Loeber[1], Anja Kniest[1], Alexander Diehl[1], Karl Mann[1] and Bernhard Croissant[2]

[1]Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Mannheim, University of Heidelberg, Germany
[2]Department of Psychiatry, Psychotherapy and Psychosomatics, Teaching Hospital Sigmaringen, University of Tuebingen, Germany

Abstract: *Objectives:* In the present study, we investigated whether buprenorphine as a partial μ-opioid receptor agonist is associated with less cognitive impairment than methadone. *Methods:* Neuropsychological functioning of opioid-dependent patients, previously assigned to methadone (MMP, n = 30) or buprenorphine (BMP, n = 26) maintenance treatment according to their own preference, was compared and dose effects were investigated. *Results:* MMP and BMP performed equally well on all measures of neuropsychological functioning including the trail making test, the continuous performance test, and a vigilance task. However, patients receiving a higher dose of methadone were impaired in a vigilance task. *Conclusions:* In a free-choice administration of methadone or buprenorphine, there seems to be no difference in cognitive functioning. Possible explanations are discussed.

Keywords: Buprenorphine, cognitive impairment, Maintenance treatment, methadone, vigilance

INTRODUCTION

Methadone maintenance treatment is the most widely used substitution treatment in Europe (1) and the United States (2) and its effectiveness with respect to the reduction of drug-associated harm and the improvement of abstinence

Address correspondence to PD Bernhard Croissant, M.D., M.A., Head of Department, Teaching Hospital Sigmaringen, Department of Psychiatry, Psychotherapy and Psychosomatics, University of Tuebingen, Hohenzollernstrasse 40, D-72488 Sigmaringen, Germany. E-mail: b.croissant@klksig.de

rates has been clearly demonstrated (3). However, recent studies (4, 5, 6, 7, 8, 9) suggest that methadone maintenance treatment may induce significant cognitive impairments. Since further studies have shown that opiate-induced cognitive impairment of addicted patients may contribute to treatment success (e.g. (10, 11)), these results underline the importance of alternative pharmacological treatment options to methadone maintenance treatment.

Buprenorphine has been introduced into clinical practice as an alternative to methadone and is meanwhile well established in maintenance treatment (12, 13, 14). However, in their meta-analysis, Barnett et al. (15) state that further research is necessary to determine patients' characteristics and to distinguish specific settings where buprenorphine maintenance treatment is more effective than methadone maintenance treatment.

Several authors have suggested that buprenorphine, as a partial μ-opioid receptor agonist (16), may be associated with reduced sedation and impairment of psychomotor and cognitive performance. In line with this, the results of several dose effect studies (e.g. (17, 18, 19, 20)) show that buprenorphine only mildly impairs gross motor performance and does not influence more complex cognitive functions [20]. In addition, further studies demonstrated a better performance of patients maintained on buprenorphine compared to methadone with respect to attention and verbal memory (21) as well as decision making (22). In contrast, Soyka et al. (23) did not find evidence for better performance of opiate dependent patients randomly assigned to buprenorphine-maintenance treatment.

One reason for the conflicting results might be the random assignment to different treatment conditions. While randomized control trials may reveal that a substance is associated with less cognitive impairment, it is important to take individual variation regarding treatment response into account. Further, treatment compliance of opioid-dependent patients is generally low when the preferred treatment is not granted, and therefore uncontrollable effects due to the consumption of further substances or loss of follow-up data are likely.

Thus, the aim of the present study was to compare neuropsychological functioning of opioid-dependent outpatients allocated to either buprenorphine or methadone maintenance treatment based on their own preferences. As previous studies reported dosage effects of methadone (8) and buprenorphine (20), we further investigated whether the methadone and buprenorphine doses were related to cognitive impairment. In addition, we compared these patients to healthy controls by providing normative data where possible.

METHODS

Subjects

Opiate dependent patients according to DSM-IV-criteria were recruited from July 2005 to December 2006 from an outpatient substitution treatment

facility for opiate dependence. All patients that matched the inclusion criteria and did not fulfil any of the exclusion criteria were asked to participate in the study. During the recruitment period, this allowed for the inclusion of 30 patients undergoing methadone maintenance treatment and 24 patients undergoing buprenorphine maintenance treatment. Heroin was the substance that was primarily abused by patients and was administered through injection by all subjects. Allocation to methadone or buprenorphine maintenance treatment was based on the patients' preferences after being comprehensively informed about methadone and buprenorphine by their physician. Patients were only included in the study if they were on a stable dose of methadone or buprenorphine for at least fourteen days. Weekly contacts with an experienced physician were supplied. To avoid confounding acute drug effects, patients had to refrain from other substance consumption, especially opiates, benzodiazepines, amphetamines, cocaine, and alcohol on the day of testing. This was controlled by urine tests (von Minden GmbH, Moers, Germany) and breath analysis (Draegerwerk AG, Luebeck, Germany) prior to neuropsychological testing. Exclusion criteria were current episodes of major depression and anxiety disorders, current or previous psychotic episodes, and current application of antidepressants or other psychotropic medication. The study was approved by the local ethics committee of the University of Heidelberg; all patients signed written informed consent.

Testing Procedure

Testing was performed after the patients had received their normal daily dose of methadone or buprenorphine and lasted approximately 2 hours. It started with the assessment of sociodemographic data, a standardized interview to assess drug history and the application of the General Depression Scale (24) to assess depressive symptoms. Comprehensive neuropsychological testing was performed 30 minutes after application of methadone or buprenorphine to provide a sufficient blood concentration of pharmacological agents (25, 26).

Neuropsychological testing comprised several tasks sensitive to three different attention factors (27, 28). *Vigilance and sustained attention* as the first factor involves the allocation of attention resources over time and was assessed with VIGIL, (29), the Continuous Performance Test from the Gordon Diagnostic System (http://www.gsi-add.com/index.htm) and a Visual Analogue Scale. *Selecting and focusing of sensory stimuli* comprises processes of filtering, selecting, and focusing of sensory stimuli and was assessed with the d2-test (30). By contrast, intention generating and response execution processes are necessary for *response selection and control* and were assessed with the Trail Making Test (TMT) (31) and the Determination Test in a German version (DT) (29). In addition, the California Verbal Learning Test (CVLT) (32) was administered to assess memory function. Further details are available from the authors.

The order of the neuropsychological tests was not randomized but designed to alternate between tasks with different demands on concentration. All patients completed the tests in the same order.

Statistical Analysis

Differences between MMP and BMP regarding demographic and substance related variables were analyzed using chi-square analysis for categorical variables and t-tests for continuous variables. Neuropsychological tests were compared across the two groups using *t*-tests. If assumption of homogeneity of variances was violated, results were corrected and adjusted degrees of freedom are reported. All tests considered an alpha level of $p < .05$; Bonferroni-adjustments were applied. Any demographic or substance-related variable that significantly differed between groups, and was correlated with a neuropsychological variable, was entered into a subsequent analysis of covariance. Dose effects were analyzed by correlating the dose of either methadone or buprenorphine with measures of cognitive functioning separately for each treatment group. Patients' individual scores were transformed into percentile ranks (PR) based on age and gender to provide a comparison with normative data. SPSS for Windows (Version 15.0.0) was used for all statistical analyses.

RESULTS

Patients

The total sample of the present study consisted of 54 opiate dependent outpatients (15 women and 39 men), aged between 19 and 52. There were no significant differences between MMP and BMP with respect to gender, age, years of education, intelligence (assessed with a vocabulary test (33)), and further demographic and substance related variables (see Table 1). However, we found a trend towards a significantly higher number of head injuries, defined as an episode of unconsciousness associated with hospitalization, in MMP compared to BMP ($t(30) = 1.9$, $p < .10$; 95% CI -.04 – 1.2).

Neuropsychological Test Battery

Our results show that MMP and BMP performed equally well on all measures of neuropsychological functioning. We found no statistically significant group differences for any of the measures (see Table 2).

Table 1. Demographic- and substance-related characteristics of methadone-maintained patients (MMP) and buprenorphine-maintained patients (BMP)

	MMP (n = 30)	BMP (n = 24)	Level of significance
Gender			
women [N(%)]	7 (23.3)	8 (33.3)	
men [N (%)]	23 (76.7)	16 (66.7)	n.s.
Age (years) [Mean (SD)]	35.0 (7.6)	36.5 (8.5)	n.s.
Patients in a relationship [N(%)]	15 (50.0)	15 (62.5)	n.s.
Years of education (years) [Mean (SD)]	11.5 (2.4)	12.4 (2.3)	n.s.
Patients employed [N(%)]	13 (43.3)	13 (54.2)	n.s.
Duration of opiate dependence (years) [Mean (SD)]	14.3 (7.9)	14.7 (9.5)	n.s.
Duration of substitution treatment in total (years) [Mean (SD)]	4.3 (4.1)	3.1 (2.0)	n.s.
Drug treatment dose (mg/day) [Mean (SD)]	74.3 (30.9)	9.4 (3.6)	N/A
Positive family history of substance dependence [N(%)]	12 (40.0)	11 (45.8)	n.s.
Number of opiate overdoses [Mean (SD)]	1.7 (4.0)	1.1 (2.5)	n.s.
Number of head injuries [Mean (SD)]	.6 (1.6)	.04 (0.2)	$p < .10$
General depression scale (ADS; summary score) [Mean (SD)]	11.3 (5.6)	13.0 (7.4)	n.s.
IQ (WST) [Mean (SD)]	93.8 (10.7)	91.8 (9.0)	n.s.

n.s.: group difference not statistically significant; N/A: not applicable.

Analysis of Covariance

Although only a few patients reported head injuries, we found a weak trend towards a significant difference between the two treatment groups, and the number of head injuries was significantly correlated with the outcome score of part A and B of the TMT in the complete sample ($r = .48$, $p < .001$ and $r = .43$, $p < .01$, respectively). Entering the number of head injuries as a covariate in an analysis of covariance, we found that the number of head injuries had a

Table 2. Neuropsychological functioning of methadone-maintained patients (MMP) and buprenorphine-maintained patients (BMP)

	Mean (SD)		
	MMP (n = 30)	BMP (n = 24)	Level of significance
Vigilance and sustained attention			
VIGIL, no. correct responses	95.2 (6.6)	96.7 (4.1)	n.s.
VIGIL, no. errors	4.1 (6.6)	4.3 (6.4)	n.s.
VIGIL, reaction time correct responses	.5 (.1)	.5 (.1)	n.s.
CPT, no. correct responses	37.6 (8.7)	39.8 (4.3)	n.s.
CPT, no. errors	3.1 (4.8)	4.3 (5.6)	n.s.
CPT, reaction time correct responses	210.2 (95.4)	180.2 (67.8)	n.s.
VAS	8.0 (1.9)	7.4 (2.3)	n.s.
Selecting and focusing of sensory stimuli			
d2, concentration	381.0 (68.7)	359.3 (76.8)	n.s.
Response selection and control			
TMA, total seconds	31.2 (14.9)	32.1 (10.5)	n.s.
TMB, total seconds	83.7 (38.3)	88.2 (38.4)	n.s.
DT, no. correct responses	206.5 (26.3)	211.2 (32.4)	n.s.
DT, no. errors	15.0 (11.9)	13.1 (11.8)	n.s.
DT, reaction time total	.9 (.1)	.9 (.1)	n.s.
Memory			
CVLT short-delay free recall, no. correct answers	10.8 (3.4)	11.8 (2.6)	n.s.
CVLT long-delay free recall, no. correct answers	11.2 (3.3)	12.5 (2.4)	n.s.
CVLT, recognition hits	15.0 (1.1)	15.1 (1.3)	n.s.

VIGIL: computerized vigilance test; CPT: Continuous Performance Test 1–9; VAS: Visual Analogue Scale; d2: d2-Test; TMA: Trail Making Test Part A; TMB: Trail Making Test Part B; DT: Determinations test; CVLT: California Verbal Learning Test; n.s.: not statistically significant group difference.

significant effect on performance in part A ($F(1) = 17.14$, $p < .001$) as well as part B ($F(1) = 13.24$, $p < .01$) of the TMT. The effect of treatment group on performance was not significant when the effect of the number of head injuries was controlled for ($F(1) = 1.57$, $p =$ n.s. for part A and $F(1) = 1.70$, $p =$ n.s. for part B). Thus, this result confirmed our previous analysis, that there is no

relevant difference of MMP and BMP on possible cognitive impairment, but the number of head injuries.

Dose Effects

The buprenorphine dose was not significantly correlated with any of the cognitive variables. In contrast, we found a significant negative correlation between the methadone dose and the number of correct responses ($r = -.49$, $p < .01$) and a significant positive correlation with the mean reaction time for correct responses in the vigilance task VIGIL ($r = .40$, $p < .05$). These results indicate that cognitive impairment increases with the increase of the administered methadone dose.

Comparison with Normative Data

The distribution of the PR of MMP and BMP shows that opiate dependent-patients perform worse than most subjects in the normative control samples regarding several measures of *Vigilance and sustained attention*, *Selecting and focusing of sensory stimuli*, and *Response selection and control* (*MMP:* median (PR) d2 = 16, median (PR) Trail Making Test Part B (TMB) = 20, median (PR) DT, no. correct responses = 29, median (PR) VIGIL, no. correct responses = 30, median (PR) VIGIL, no. errors = 35; *BMP:* median (PR) d2 = 13, median (PR) TMB = 20, median (PR) DT, no. correct responses = 34, median (PR) VIGIL, no. correct responses = 30, median (PR) VIGIL, no. errors = 35).

DISCUSSION

The results reported in the present article suggest that buprenorphine maintenance treatment for opiate-dependent patients is not associated with less cognitive impairment when compared with methadone maintenance treatment in a treatment schedule providing the administration of methadone or buprenorphine treatment according to patients' preferences.

Based on the assumption that the partial μ-opioid receptor agonist buprenorphine may be associated with less sedation and impairment of psychomotor and cognitive performance, we administered several neuropsychological tests and a subjective measure to assess different aspects of vigilance and sustained attention, selecting and focusing of sensory stimuli, response selection and control, and memory functioning. Although the comparison with normative data revealed that both samples were impaired, we found no differences between BMP and MMP regarding the applied measures of neuropsychological functioning. These results are in line with findings reported

by Soyka et al. (26). Although some studies reported differences between patients maintained on buprenorphine or methadone in attention and verbal memory (21), as well as decision making (22), in these studies no significant differences are found regarding the neuropsychological tests of intellectual capacity and prefrontal cortical functioning (21, 26). Thus, our results are in line with these latest findings and provide new evidence for the equivalence of buprenorphine-maintenance treatment and methadone-maintenance treatment regarding neuropsychological functioning.

However, as has been reported before (8, 20), higher doses of methadone seem to be related to impairment of vigilance and memory functioning, whereas this seems only to be true for buprenorphine administered at doses higher than according to usual clinical considerations (20).

In our study, the administration of buprenorphine or methadone followed patients' preferences. Thus, although our comprehensive assessment of demographic and substance-related variables showed no differences between the two treatment groups, we cannot rule out that our results are subject to uncontrolled effects. However, we think that the allocation to different treatment options based on patients' preferences provides valuable data in addition to randomized control trials taking into account individual differences in treatment response as has been shown previously (34). In addition, a comparison with normative data shows that opiate dependent-patients perform worse than most subjects in the normative control samples in our measures of neuropsychological functioning. The daily doses of methadone and buprenorphine administered in our study were in the higher range of those mentioned in other studies (e.g., (5, 22)), thus underdose is not in question.

Further studies are required to investigate the effects of methadone and buprenorphine maintenance treatment, especially regarding dose dependent effects, since high to very high doses of both substances seem to have the potential to ameliorate cognitive functioning.

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