

Effect of long-term sustained release naltrexone on semantic recognition of opioid addicts**☆

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Abstract

BACKGROUND: Long-term sustained release naltrexone has been reported in clinical application near one year that it can improve emotional state and relieve addiction; therefore, the effect of long-term sustained release naltrexone on memory restoration at neuropsychology level were explored.

OBJECTIVE: To observe the effect of long-term sustained release naltrexone on memory ability of opioid addicts.

DESIGN, TIME AND SETTING: A contrast observational study was performed at Drug Rehabilitation Centers of Wuhan, Changde, Zhengzhou, and Jiangyang between October and December 2006. Healthy controls were tested in Shenzhen Hospital of Peking University in October 2006.

PARTICIPANTS: A total of 88 males with opioid addicts were divided into naltrexone group ($n=35$), compulsory detoxification group ($n=26$), and non-treatment group ($n=27$). Another 22 healthy subjects were considered as the controls.

METHODS: At 6–12 months before testing, naltrexone (3.1 g) was subcutaneously implanted into bilateral abdominal wall in the naltrexone group; patients in the compulsory detoxification group underwent completely compulsory detoxification for 6 months, and the examination results, including diamorphine, methadone, and buprenorphine in urine, were negative on the immediately testing day. Event related potential and its wave form were recorded from the opioid addicts in the three groups and from healthy controls who finished semantic recognition between new and old words using portable-type event related potential working system.

MAIN OUTCOME MEASURES: Correct rate and response time of semantic memory; latency and amplitude of language related potential-N400.

RESULTS: ① There were significant differences in correct rate and response time between three experimental groups and healthy control group ($P < 0.001$); in addition, correct rate was significantly increased, and response time was significantly shortened in the naltrexone group compared to compulsory detoxification group and non-treatment group ($P < 0.05$). ② N400 latency in the three experimental groups was significantly longer than healthy control group ($P < 0.01$), while N400 amplitude in the naltrexone group was increased, which was no significant difference compared to healthy control group ($P > 0.05$) but was significant difference compared to compulsory detoxification group and non-treatment group ($P < 0.01$).

CONCLUSION: Long-term sustained release naltrexone can effectively improve neural function and enhance semantic memory of the opioid addicts.

INTRODUCTION

By pharmacological action, opioid drugs cause hyperhedonia, dependence, and tolerance in the brain^[1-2]. Otherwise, drug abuse for a long term can induce changes of affection, consciousness, and cognitive function^[3-7]. Naltrexone can resist hyperhedonia, relieve dependent feeling, and decrease relapse rate^[8-14]. However, few of references reported whether naltrexone can positively influence advanced cognitive function of injured brain. Therefore, emotional words selected from Chinese Emotional Words Bank of Psychology Institute of Chinese Academy of Science were used for active memorization and recognition so as to check semantic memory ability; furthermore, event related potential was recorded to analyze the effect of long-term sustained release naltrexone on semantic recognition of opioid addicts according to differences of wave form.

SUBJECTS AND METHODS

Design

A contrast observational study.

Time and setting

This study was performed at Drug Rehabilitation Centers of Wuhan, Changde, Zhengzhou, and

Jiangyang between October and December 2006. Healthy controls were tested in Peking University Shenzhen Hospital in October 2006.

Subjects

Opioid addicts collected from Hubei, Hunan, and Guangdong provinces had administrating history of opium, morphine, heroin, and methadone. There were 88 males, aging 21–34 years, with the mean age of (24.1±4.3) years, opioid history of 1–17 years, with the mean history of (9.85±3.81) years, and voluntary and compulsory detoxification for 2–120 times (median = 15 times). All patients were diagnosed according to *Chinese Classification and Diagnostic Criteria of Mental Disorders* (CCMD-3, 10.X3) and *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, 304)^[15]. Patients did not have history of neurological or mental disorders before drug abuse but had normal eyesight or corrected eyesight and right handedness. A total of 88 opioid addicts were divided into three groups: ① Naltrexone group ($n=35$): Long-term sustained release naltrexone was provided by Siwo Life Science and Technology Company, Shenzhen, composing of naltrexone and poly lactic acid. Long-term sustained release naltrexone (3.1 g) was subcutaneously implanted into bilateral abdominal wall, and the release effect lasted for 12 months. The implantation was performed at 6–12 months before testing. Patients underwent the implantation voluntarily,

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and they would try to administrate opioid after out of hospitalization but compulsorily gave up due to feeling no hyperhedonia. On the immediately testing day, drug release lasted for 6–12 months, with the mean release of (7.6 ± 0.25) months, and the concentration of naltrexone was $1.57 - 26.11 \mu\text{g/L}$, with the mean concentration of $(10.01 \pm 5.67) \mu\text{g/L}$. Uronoscopy was performed irregularly. The checking outcomes of heroin, methadone, and buprenorphine were negative. ② Compulsory detoxification group ($n=26$): Opioid addicts collected from Compulsory Detoxification Center of Huhan underwent completely compulsory detoxification for 6 months. The checking outcomes of heroin, methadone, and buprenorphine were negative. ③ Non-treatment group ($n=27$): They underwent detoxification voluntarily, and the checking outcomes of heroin, methadone, and buprenorphine were positive due to drug abuse. Another 22 male healthy subjects collected from Peking University Shenzhen Hospital, were considered as the controls, matching with three experimental groups [23.1 ± 3.5 years old, $P > 0.05$]. The checking outcomes of heroin, methadone, and buprenorphine were negative. All the controls did not have history of smoking and drinking and neurological or mental disorder, but they had normal eyesight or corrected eyesight and right handedness.

Methods

Stimulation pictures and experimental procedures

A total of 180 emotional words were chosen from Chinese Emotional Words Bank of Psychology Institute of Chinese Academy of Science. Among them, 90 words were randomly ordered for 6 times using E-Prime software, focusing on active memorization. Five minutes after rest, all words were mixed together and randomly ordered using E-Prime software, focusing on recognition. Z represented the known words using left hand, and M represented the new words using right hand.

Data collection and processing

BrainProduct (BP-ERP) was made in Germany^[7], and 64-electric polar cap was installed using international 10–20 electroencephalogram (EEG) system. Serial EEG was collected. Two wave forms were obtained by processing and overlapped using Brain Analysis software which induced by different stimulation words. N400 (negative wave with latency of 400 ms) was considered as researching index which were located in anterior part of brain and temporal lobe. A total of 14 electrode sites were collected from Fz of prefrontal lobe, FP1, F5, FC5, C5 and T3 on the left side, FP2, F6, FC6, C6, and T4 on the right side, FPz, FCz, and Cz at median so as to analyze wave peak and latency of N400. Measure window was set at 50 ms from left and right mean wave peak.

Main outcome measures

Latency and amplitude of N400^[16-18].

Design, enforcement, and evaluation

This study was designed by the first, second, and third authors, conducted by the first author, and evaluated by all authors.

Statistical analysis

SPSS 10.0 software was used in this study. According to MANONA method, two independent variances included subject

groups (four levels, *i.e.*, naltrexone group, compulsory detoxification group, non-treatment group, and health control group); words (two levels, *i.e.*, new and old words), and dependent variance (latency and amplitude of Fz, and other electrodes) were obtained to detect latency and amplitude of N400. Based on significance of *F* value, inter-group variances were compared with Scheffe test following Post Hoc comparison. In addition, response time and correct rate were compared with One-way ANOVA method.

RESULTS

Quantitative analysis of participants

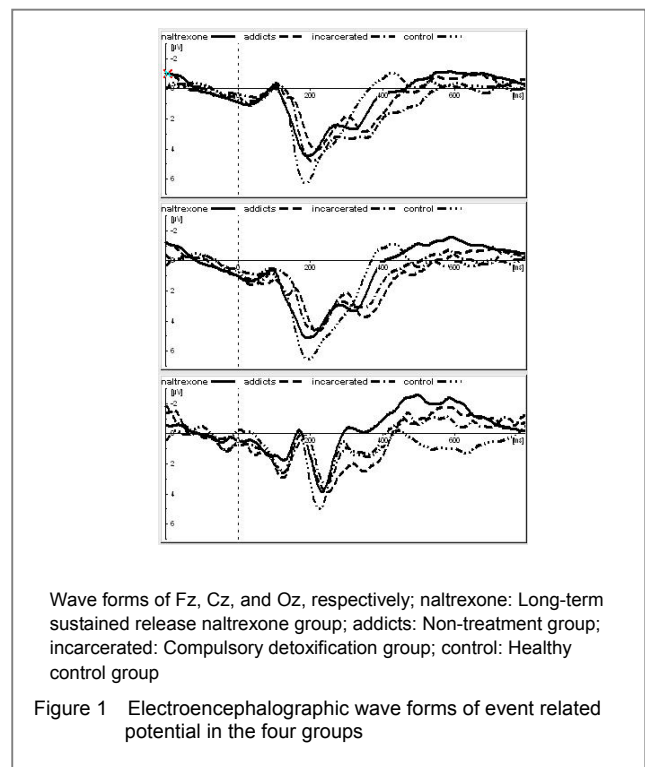
All 88 patients and 22 healthy controls were included in the final analysis.

Behavioral data

According to One-way ANOVA method, there was significant difference in response time among the four groups [$F(3, 106)=12.031, P < 0.001$]. Post Hoc suggested that response time was the shortest in the healthy control group, but the response time was prolonged in the three experimental groups ($P < 0.001$), in particular, response time was the longest in the non-treatment group. On the other hand, there was also significant difference in correct rate among the four groups [$F(3, 106)=26.023, P < 0.001$]. Post Hoc suggested that the correct rate was the highest (93.23%) in the healthy control group, which was significant difference compared to other three experimental groups ($P < 0.001$). Correct rate was 78.42% in the naltrexone group, 72.36% in the compulsory detoxification group, and 70.98% in the non-treatment group ($P < 0.05$).

Latency and amplitude of N400

The grand average of four groups is shown in Figure 1.



Mean latency of N400 is shown in Table 1.

Table 1 Latency of N400 in the four groups ($\bar{x} \pm s$, ms)

Group	n	New words	Recognition of known words
Healthy control	22	382.00±45.39	398.64±53.12
Naltrexone	35	456.64±51.56	447.73±48.59
Compulsory detoxification	26	442.09±51.96	439.82±53.48
Non-treatment	27	427.82±80.39	455.18±53.25

MANONA Analysis showed that there was significant difference in memory ability among the four groups [$F(3, 212)=10.960, P < 0.001$]. Post Hoc suggested that latency in the healthy control group was significantly shorter than naltrexone group, compulsory detoxification group, and non-treatment group ($P < 0.01$).

Mean amplitude of N400 is shown in Table 2.

Table 2 Amplitude of N400 at Fz site in the four groups (μV)

Group	n	New words	Recognition of known words
Healthy control	22	-2.149	-3.577
Naltrexone	35	-1.641	-2.455
Compulsory detoxification	26	-0.185	-1.056
Non-treatment	27	-0.600	-0.620

Main effect at different electrode sites was detected using MANONA analysis.

At Fz site, the main effect was $F(3, 212)=4.081 (P < 0.01)$. Post Hoc suggested that there were significant difference among healthy control group, compulsory detoxification group, and non-treatment group ($P < 0.01$); in addition, there was no significant difference in amplitude of N400 between naltrexone group and healthy control group ($P > 0.05$), but the value of naltrexone group was higher than compulsory detoxification group and non-treatment group.

The main effect was $F(3, 212)=4.251 (P < 0.01)$ at FCz site and $F(3, 212)=5.685 (P < 0.01)$ at Cz site. Post Hoc suggested that there were significant difference between healthy control group and non-treatment group ($P < 0.05$); in addition, amplitude of N400 in the healthy control group was higher than non-treatment group.

The main effect was $F(3, 212)=5.648 (P < 0.01)$ at FP1 site, $F(3, 212)=4.608 (P < 0.01)$ at FP2 site, $F(3, 212)=5.185 (P < 0.01)$ at F5 site, $F(3, 212)=4.559 (P < 0.01)$ at F6 site, $F(3, 212)=6.152 (P < 0.01)$ at T3 site, $F(3, 212)=4.869 (P < 0.01)$ at T4 site, and $F(3, 212)=6.314 (P < 0.01)$ at FC5 site. Post Hoc suggested that there were significant difference between naltrexone group and non-treatment group ($P < 0.01$); in addition, amplitude of N400 in the naltrexone group was higher than non-treatment group.

DISCUSSION

Emotional words selected to check semantic memory ability. Language related potential-N400 was considered as the researching index to investigate the effect of long-term sustained release naltrexone on memory ability^[16-18]. N400 is an endogenous component of ERP and it is also a negative wave to reflect cognitive processing of cerebral cortex to language; in addition, cognitive processing of language can be described *via*

multiple dimensions, such as amplitude, latency, and scalp distribution of N400; therefore, it is an objective method for cognitive processing of language. N400 has been frequently used for checking language disorder and it gradually becomes an objective mark to determine language and cognitive disorder^[19-20].

Behavioral data in this study demonstrated that response time in the three experimental groups was longer than the healthy control group, suggesting that opioid could damage memory ability of neural system. Zhang *et al*^[5] found by evaluating memory ability of opioid addicts that abnormal rate of the opioid addicts was 26.3%, which was significantly higher than healthy control group (3.8%), suggesting that memory ability of opioid addicts was damaged to a certain degree. Zhang *et al*^[7] thought that opioid could affect memory function, and the effect showed a dosage-dependence. Results in this study were generally coincidence with the references. Correct rate of word memory showed that opioid could severely damage brain function, and memory ability was obviously decreased. However, this study also achieved that response time in the naltrexone group was shorter than compulsory detoxification group and non-treatment group, and correct rate was significantly increased, suggesting that long-term sustained release naltrexone could improve memory function to a certain degree.

Recent research suggests that decreasing of amplitude and prolongation of latency are major manifestations of cognitive impairment at neural electrophysiology level. This study showed that N400 latency in the three experimental groups was longer than healthy control group, suggesting opioid could severely damage cognitive processing of language. Amplitude of N400 also suggested that there was no significant difference between naltrexone group and healthy control group, but amplitude of N400 in the compulsory detoxification group and non-treatment group was significantly lower than healthy control group, suggesting that long-term sustained release naltrexone could relieve cognitive impairment to a certain degree. Although latency of N400 was not improved after long-term sustained release naltrexone treatment, amplitude was increased greatly. Six months after long-term sustained release naltrexone treatment, amplitude of N400 was closed to healthy adults, suggesting that naltrexone could improve memory ability to a certain degree. Previous studies indicated that naltrexone could delay expression of c-fos proto-oncogene, inhibit apoptosis of neurocytes, protect neural system, and improve cerebral function of opioid addicts^[21-24].

In a word, long-term sustained release naltrexone can effectively improve semantic memory restoration of the opioid addicts to a certain degree, suggesting that long-term sustained release naltrexone not only resists opioid reaction, but also assists functional improvement of brain.

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长效纳曲酮缓释剂与阿片类药物依赖者的词语再认**☆

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摘要

背景: 长效纳曲酮缓释剂临床应用近1年后, 若干报道结果证明患者情绪状态改善, 心瘾减退, 希望进一步探寻长效纳曲酮缓释剂戒毒对记忆力恢复的神经心理学证据。

目的: 观察长效纳曲酮缓释剂治疗对阿片类药物依赖者词语记忆能力的影响。

设计、时间及地点: 对比观察实验, 于2006-10/12在湖北省武汉市公安戒毒所、湖南省常德市、河南省郑州市和广东省阳江市各地自愿戒毒所完成, 健康对照组测试于

2006-10在北京大学深圳医院完成。

对象: 男性阿片依赖综合征患者 88 例, 包括长效纳曲酮缓释剂治疗组 35 例, 强制戒毒组 26 例, 未治疗组 27 例, 另选择 22 名健康志愿者作为对照组。

方法: 长效纳曲酮缓释剂治疗组在测试前 6~12 个月腹壁两侧皮下植入长效纳曲酮缓释剂 3.1 g, 强制戒毒组接受全封闭强制戒毒 6 个月, 至测试之日止现场进行尿液海洛因、美沙酮和丁丙诺啡定性检测全部为阴性。采用便携式事件相关电位工作系统于各戒毒所现场采集记录 3 组不同戒毒方式治疗的阿片类药物依赖患者以及健康对照组完成新旧词语再认记忆任务时脑电事件相关电位及事件相关电位的波形。

主要观察指标: 对词语记忆的正确率和反应时, 语言相关电位-N400 的潜伏期和波幅。

结果: ① 3 组患者对词语记忆的正确率和反应时与健康对照组比较差异有非常显著性意义 ($P < 0.001$); 长效纳曲酮缓释剂治疗组词语记忆正确率提高, 反应时缩短, 与强制

戒毒组和未治疗组比较差异有显著性 ($P < 0.05$)。② 3 组患者完成词语记忆的 N400 潜伏期比健康对照组显著延长 ($P < 0.01$); 长效纳曲酮缓释剂治疗组其 N400 的波幅提高, 与健康对照组比较差异无显著性 ($P > 0.05$), 与强制戒毒组和未治疗组相比差异有显著性意义 ($P < 0.01$)。

结论: 长效纳曲酮缓释剂治疗能有效改善阿片类药物依赖者神经系统的功能, 提高患者的词语记忆能力。

关键词: 长效纳曲酮缓释剂; 阿片依赖; 词语再认; 事件相关电位; N400

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