

# Effects of electroacupuncture combined with paliperidone palmitate long-acting injection on withdrawal symptoms and neurotransmitters in methamphetamine addicts

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**Summary. Objective.** To investigate the effects of electroacupuncture combined with paliperidone palmitate long-acting injection (PP-LAI) on withdrawal symptoms and neurotransmitters in methamphetamine (MA) addicts. **Materials and methods.** A total of 109 methamphetamine addicts, who were treated in the hospital from October 2021 to October 2022, were selected. According to the random number table, the patients were divided into the study group (n=54) and the control group (n=55), in which the control group was treated with PP-LAI and the study group was treated with electroacupuncture on the basis of the control group; the methamphetamine withdrawal symptom score scale was used to assess the therapeutic effect before treatment and within 12 months after treatment; the changes of brain neurotransmitters dopamine,  $\gamma$ -aminobutyric acid, serotonin, acetylcholine values were compared between the two groups. **Results.** 1) There was no statistical difference in MA withdrawal symptom scores between the two groups before treatment ( $p>0.05$ ); 2) MA withdrawal symptom scores have a statistically significant difference between the study group and the control group after 3 and 6 months of treatment; 3) dopamine levels in the study group were significantly higher than those in the control group after 6 months of completion of treatment, and  $\gamma$ -aminobutyric acid values and 5-serotonin values in the study group were significantly lower than those in the control group ( $p<0.05$ ). **Conclusions.** Electroacupuncture combined with PP-LAI can partially improve the withdrawal symptoms and anxiety of methamphetamine addicts. This is a potential treatment for preventing relapse of withdrawal symptoms.

**Key words.** Electroacupuncture treatment, methamphetamine, neurotransmitters, paliperidone palmitate long-acting injection.

## Introduction

Methamphetamine (MA), commonly known as amphetamine chloride, is an amphetamine-type

*Effetti dell'elettroagopuntura combinata con paliperidone palmitato a rilascio prolungato sui sintomi di astinenza e sui neurotrasmettitori nei tossicodipendenti da metanfetamina.*

**Riassunto. Scopo.** Sono stati studiati gli effetti dell'elettroagopuntura combinata con paliperidone palmitato a rilascio prolungato (PP-LAI) sui sintomi di astinenza e sui neurotrasmettitori nei tossicodipendenti da metanfetamina. **Materiali e metodi.** Sono stati selezionati un totale di 109 tossicodipendenti da metanfetamina (MA) che sono stati curati in ospedale da ottobre 2021 a ottobre 2022. Secondo la tavola di numeri casuali, i pazienti sono stati divisi nel gruppo di studio (n=54) e nel gruppo di controllo (n=55): il gruppo di controllo è stato trattato con PP-LAI e il gruppo di studio è stato trattato con elettroagopuntura sulla base del gruppo di controllo; la scala del punteggio dei sintomi di astinenza da metanfetamina è stata utilizzata per valutare l'effetto terapeutico prima del trattamento ed entro 12 mesi dopo il trattamento; tra i due gruppi sono state confrontate le variazioni dei valori dei neurotrasmettitori cerebrali dopamina, acido  $\gamma$ -aminobutirrico, serotonina e acetilcolina. **Risultati.** 1) Non è stata riscontrata alcuna differenza statistica nei punteggi dei sintomi di astinenza da MA tra i due gruppi prima del trattamento ( $p>0,05$ ); 2) i punteggi dei sintomi di astinenza da MA presentano una differenza statisticamente significativa tra il gruppo di studio e il gruppo di controllo dopo 3 e 6 mesi di trattamento. 3) I livelli di dopamina nel gruppo di studio erano significativamente più alti di quelli del gruppo di controllo dopo 6 mesi dal completamento del trattamento e i valori di acido  $\gamma$ -aminobutirrico e di 5-serotonina nel gruppo di studio erano significativamente inferiori a quelli del gruppo di controllo ( $p<0,05$ ). **Conclusioni.** L'elettroagopuntura combinata con PP-LAI può parzialmente migliorare i sintomi di astinenza e l'ansia dei tossicodipendenti da metanfetamina. Si tratta di un potenziale trattamento per prevenire la ricaduta dei sintomi di astinenza.

**Parole chiave.** Metanfetamine, neurotrasmettitori, paliperidone palmitato a rilascio prolungato, trattamento con elettroagopuntura.

central nervous stimulant<sup>1</sup>. The low methylenedioxy-methamphetamine (MDMA) doses can be used in post-traumatic stress disorder as support for assisted psychotherapy<sup>2</sup>. The MDMA addiction might be

multidimensional with an onset in earlier years. The methamphetamine, along with cannabis, psilocybin, mescaline, and psychostimulants, were associated with hallucinogen-persisting perception disorder (HPPD)<sup>3</sup>. MA has a strong addictive effect on cerebral blood flow, glucose metabolism, and neurotransmitters in users<sup>4</sup>, which produces a strong euphoric effect by increasing extracellular dopamine levels. After drug addiction treatment, somatic withdrawal symptoms such as headache, fatigue, insomnia or drowsiness, and increased appetite are mild<sup>5</sup>, and these symptoms will be relieved within 1 to 2 weeks after withdrawal, while mental dependence is stronger and negative emotional symptoms are more pronounced after withdrawal, which is the main reason for re-use in most patients<sup>6</sup>. Domestic studies suggest that acupuncture at Neiguan, Shenmen, Zusanli, Sanyinjiao, and Huatuo Jiaji points has a therapeutic effect on opioid withdrawal symptoms<sup>7</sup>. Paliperidone palmitate long-acting injection (PP-LAI) is an atypical antipsychotic long-acting injection that can be hydrolyzed to paliperidone in the body and acts on MA addicts by modulating neurotransmitters on central dopamine D2 receptors and 5-hydroxytryptamine 2 receptors<sup>8-10</sup>. The paliperidone palmitate is commonly used in the treatment of schizophrenia, with formulations that are monthly, 3-months and 2 years<sup>11,12</sup>. Physiologically, Methamphetamine activates microglia in a dose-dependent manner and via a time course that is generally concurrent with damage to the dopaminergic system<sup>13</sup>. As a possible target for methamphetamine's effects on microglia, the microglial-specific fractalkine receptor (CX3CR1), a mediator of 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP)-induced neurodegeneration of dopamine neurons<sup>14</sup>, was evaluated for a role in methamphetamine-induced microglial activation and neurotoxicity. It effectively improves psychiatric

symptoms and mood symptoms, such as anxiety and depression, that occur during MA withdrawal and is a key factor in promoting recovery and inhibiting relapse in MA addicts<sup>15</sup>.

We have previously found that PP-LAI combined with electroacupuncture is superior to electroacupuncture alone in the treatment of methamphetamine addicts and significantly improves anxiety, depression, and brain waves, thereby preventing relapse in addicts, but the mechanism by which it acts is unclear<sup>15</sup>. Therefore, based on previous studies, this study investigated the effects of electroacupuncture combined with PP-LAI on withdrawal symptoms and neurotransmitters in methamphetamine addicts based on the theory of integrated traditional Chinese and Western medicine treatment, and the results are reported as follows.

## Materials and methods

### STUDY SUBJECTS

A total of 130 MA addicts treated in hospital from January 2020 to December 2020 were selected. We screened 130 patients, excluding 10 patients who refused to participate and 11 patients who did not meet the inclusion and exclusion criteria. Ultimately, 109 patients were included in this study. The patients were divided into the control group (n=55) and study group (n=54) according to treatment methods (figure 1). The occurrence or presence of less than 3 incidents in the previous 12 months is a diagnosis of MA abuse addiction. 1) There is a strong desire for MA and compulsive drug-seeking behavior. 2) It is difficult to control MA abuse's beginning, end, and dosage. 3) Withdrawal symptoms occur when MA is reduced or stopped. 4) Increased tolerance. 5) The original interest gradually lost, affecting family and social relations. 6) Stubbornly

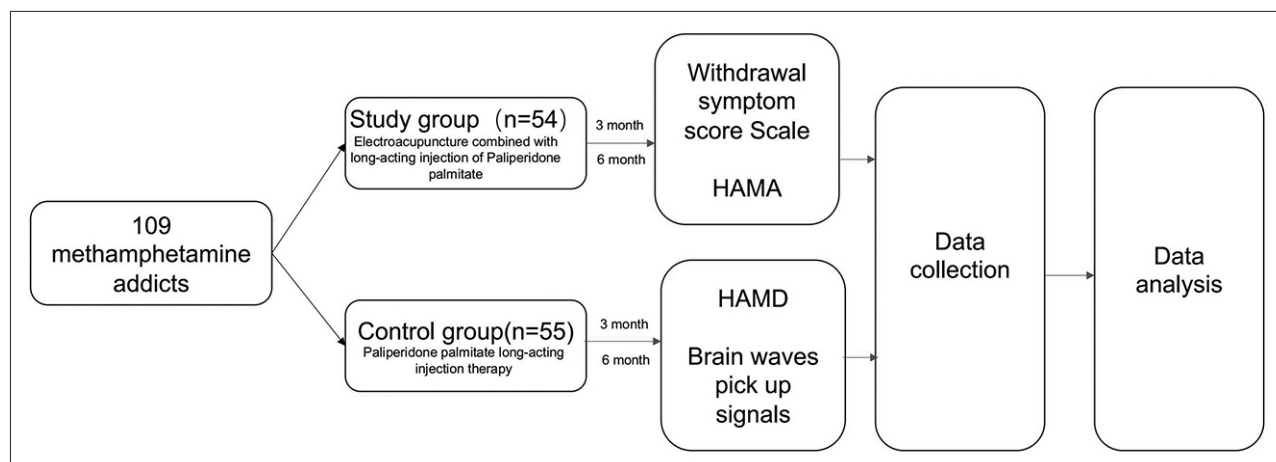


Figure 1. The participant flowchart for this study.

abusing MA regardless of physical damage and social harm. Exclusion criteria: 1) allergic history to the drugs used in this study; 2) combined with heart, liver, lung, kidney and other serious organ diseases; 3) lactating or pregnant women; 4) cannot continue treatment due to external factors; 5) physician determined intellectual disability. In order to exclude the interference of other factors, we selected the study group and the control group members to meet the requirements of gender and age control. All patients gave informed consent to participate in this study, and this study was approved by the Medical Ethics Committee of Wuhan Wudong hospital (No. WDYYLL202102).

## METHODS

A semi-structured interview was adopted for the screening and diagnosis of mental disorders. One-to-one face-to-face questions and answers were conducted in the order of topics, lasting 30-60 minutes. Only after organic brain disorders and mental disorders caused by physical diseases were excluded could the diagnosis of mental disorders caused by psychoactive substances be confirmed.

The control group was treated with electroacupuncture. Bilateral Neiguan, Shenmen, Zusanli, Sanyinjiao and Huatuo Jiaji points were taken, and the needle was inserted by one-handed needle insertion method, 0.5 ~ 0.8 inches was inserted. Each needle was connected to a low-frequency electronic pulse therapeutic apparatus (model: G6805-2B; purchased from Shanghai Huayi Co., Ltd.), and a continuous pulse wave was selected, with a stimulation frequency of 2 Hz and a maximum stimulation intensity acceptable to the patient, and the needle was left in place for 20 min. The treatment was performed once every other day for 3 months, for a total of 45 treatments.

The study group was treated with PP-LAI on the basis of electroacupuncture treatment in the control group, 150 mg of PP-LAI (manufacturer: Janssen Pharmaceutica N.V.; drug standard code 86979438000138) was injected on the first day, and 100 mg was injected again one week later, and the injection sites were the deltoid muscle. After the two injections, the injections were given once a month at a dose of 100 mg, and the site of injection could be either the deltoid muscle or the gluteal muscle for a treatment period of 3 months.

## OUTCOME MEASURES AND EVALUATION CRITERIA

The changes of MA withdrawal symptoms were assessed according to MA Withdrawal Symptom Scale<sup>10</sup> before treatment, at 3 months after treatment, and at 6 months after treatment in both groups. Patients were assessed on a 14-item MA withdrawal symptom rating scale, with score 1 being mild or occasional symptoms requiring no specific treatment,

score 2 being moderate symptoms, and score 3 being severe symptoms affected by the disorder for most of the day. (Note: MA Withdrawal Symptom Score and Withdrawal Symptom Score developed by Beijing University China Institute of Drug Dependence was the same scale, only MA Withdrawal Symptom Score was selected).

After 6 months of treatment, all patients were treated with ML2001 Encephalofluctograph Technology (ET) analyzer (Beijing Instruments Co., Ltd.), electrodes were placed according to the international 10-20 system, the recording time was 18 min, the sampling frequency was 256 Hz, and the time constant was 3 s. ET is a non-invasive brain function detection method developed in China recently<sup>15</sup>. Different frequency ultra-slow fluctuations in electroencephalogram waves correspond to the activity of different neurotransmitters in the brain. By displaying the fundamental frequency S-spectrum, the oscillation reaction of neurotransmitters in the brain can be reflected, and signals concerning the activity of neurotransmitters in the brain can be obtained. The obtained electroencephalogram signals are analyzed via conventional electroencephalogram analysis, followed by window setting, frequency spectrum analysis, power spectrum extraction, and temporal and spatial analysis of fine structures. Finally, the test data are converted and processed with FoxPr06.0 database software. The brain's neurotransmitters dopamine,  $\gamma$ -aminobutyric acid, and serotonin were automatically analyzed and processed by ET program.

## STATISTICAL ANALYSIS

PASS 2021 Power Analysis and Sample Size Software (NCSS, LLC. Kaysville, Utah, USA, [ncss.com/software/pass](http://ncss.com/software/pass)) was used to calculate the sample size required for the present study. The withdrawal scores of the two groups at 6-month follow-up were defined as the primary outcome and used the independent sample t test to estimate the sample size. Before the study, we conducted a preliminary experiment with a small sample and referred to the data reported in previous literatures. Group sample sizes of 7 and 7 achieve 92.341% power to reject the null hypothesis of equal means when the population mean difference is  $\mu_1 - \mu_2 = 14.8 - 2.98 = 11.82$  with standard deviations of 7.6 for control group and 1.7 for study group, and with a significance level (alpha) of 0.05 using a two-sided two-sample unequal-variance t-test. Taking into account the 20% loss of follow-up rate, the required sample size for this study was 9 people per group. SPSS 22.0 statistical software was used for data analysis. Measurement data were expressed as mean  $\pm$  variance. Means were compared by t test. Enumeration data were expressed as rate (%) and tested by

$\chi^2$  test.  $P < 0.05$  indicated statistically significant differences in results.

## Results

### COMPARISON OF METHAMPHETAMINE WITHDRAWAL SYMPTOM SCORE SCALE BETWEEN THE TWO GROUPS BEFORE AND AFTER TREATMENT

The 109 methamphetamine addicts included 55 cases in the control group and 54 cases in the study group. In the control group, there were 45 males and 10 females aged 24~46 years; DA level before treatment was 2.44 (2.14-2.74) in the control group (table 1). What's more, the expression of GABA during pre-treatment was 7.22 (6.78-7.66) in the control group. The study group consisted of 39 males and 15 females aged 25-46 years. The study group's DA level before treatment was 2.44 (2.15-2.73). The expression of GABA during pre-treatment was 7.22 (6.77-7.67) in study group (table 1).

There was no significant difference in MA withdrawal symptom scores between the study group and the control group before treatment ( $p > 0.05$ ); MA withdrawal symptom scores in the study group were significantly lower than those in the control group after 3 and 6 months of treatment, and the difference was statistically significant ( $p < 0.05$ ), as shown in table 2.

### COMPARISON OF NEUROTRANSMITTERS BETWEEN THE TWO GROUPS BEFORE AND AFTER TREATMENT

Before treatment, dopamine DA levels in the study group were compared with those in the control group, and the difference was not statistically significant ( $p > 0.05$ ). After 6 months of treatment, dopamine levels in the study group were higher than those in the control group, and the difference was statistically significant ( $p < 0.05$ ), as shown in the table 3.

Dopamine  $\gamma$ -GABA levels in the study group were compared with those in the control group before treatment, and the difference was not statistically

**Table 1.** Comparison of baseline levels between research group and control group.

	Study group (n=54)	Control group (n=55)	T value	P value
Age (years)	36.13 (25.68-46.58)	35 (24-46)	<b>0.949</b>	0.334
Gender (male/female)	39/15	45/10	<b>0.032</b>	0.5518
<b>Educational background</b>				
Primary school or lower	<b>9.26%</b> (5/54)	27.27% (15/55)	<b>7.470</b>	<b>0.011</b>
Middle school	57.41% (31/54)	60.00% (33/55)	<b>0.807</b>	<b>0.076</b>
University degree	33.33% (18/54)	12.73% (7/55)	<b>0.013</b>	<b>6.546</b>
<b>Timing</b>				
Before receiving MA treatment	25.07 (24.57-25.57)	25.08 (24.62-25.54)	<b>0.000</b>	0.989
After 3 months of MA treatment	19.05 (18.69-19.41)	19.04 (18.69-19.39)	<b>0.000</b>	0.9457
After 6 months of MA treatment	14.49 (13.89-15.09)	14.49 (13.93-15.05)	<b>0.000</b>	0.9357
DA level before treatment	2.44 (2.15-2.73)	2.44 (2.14-2.74)	<b>0.000</b>	0.9457
DA level after treatment	2.67 (2.32-2.86)	2.81 (2.42-2.97)	<b>0.000</b>	0.0248
Pre-treatment GABA levels	7.22 (6.77-7.67)	7.22 (6.78-7.66)	<b>0.000</b>	0.9781
GABA levels after treatment	7.35 (7-8.05)	7.36 (7.01-7.71)	<b>0.000</b>	0.9676
5-HT level before treatment	23.77 (22.25-25.29)	23.76 (22.23-25.29)	<b>0.000</b>	0.9572
5-HT level after treatment	20.93 (20.21-21.65)	20.96 (20.27-21.65)	<b>0.32</b>	0.7236

**Table 2.** Comparison of MA withdrawal symptom score scale between the two groups ( $x \pm s$ ).

Group	MA withdrawal symptom score before treatment (points)	MA withdrawal symptom score after 3 months (points)	MA withdrawal symptom score after 6 months (points)
Control group (n=55)	25.47±2.38	19.05±3.07	15.36±3.02
Study group (n=54)	26.05±2.27	12.05±2.19	8.41±1.08
T value	1.302	13.832	20.553
P value	0.196	0.000	0.000

significant ( $p>0.05$ ). After 6 months of treatment,  $\gamma$ -GABA levels in the study group were lower than those in the control group, and the difference was statistically significant ( $p<0.05$ ), as shown in table 3.

Before treatment, there was no significant difference in dopamine 5-HT levels between the study group and the control group ( $p>0.05$ ). After 6 months of treatment, 5-HT levels were lower in the study group than in the control group, and the difference was statistically significant ( $p<0.05$ ), as shown in table 3.

## Discussion and conclusions

Paliperidone palmitate therapy with long-acting injection combined with electroacupuncture significantly improved anxiety, depression, and brain waves in methamphetamine addicts and was beneficial in preventing relapse in addicts. In this study, we further investigated the efficacy of long-acting paliperidone palmitate combined with electroacupuncture for 3 and 6 months in treating MA withdrawal symptoms. The results showed that after treatment, the scores of MA withdrawal symptoms were significantly lower than those of the control group. After six months of treatment, MA addicts had significantly higher dopamine levels and significantly lower gamma-aminobutyric acid and serotonin values. The re-

sults of this study suggest that long-acting injection combined with electroacupuncture for paliperidone palmitate may be an effective treatment for MA withdrawal symptoms.

The withdrawal symptoms such as anxiety, depression, and sleep disorders are closely related to the "Shenming", and the combination of the acupuncture points can regulate the qi flow, tonify the qi and blood, strengthen the spleen and stomach, and calm the mind, thus regulating the patient's yin and yang balance and achieving therapeutic effects<sup>6</sup>. After quitting methamphetamine, addicts experience decreased interest, depression, anxiety, and unresponsiveness. It then shows euphoria and pleasure when the patient reuses it<sup>16</sup>. In order to judge the MA withdrawal status of patients, the MA withdrawal symptom score can be used to evaluate the withdrawal symptoms of patients from 14 aspects, including appetite, fatigue, drowsiness, desire to use drugs, somnolence, interest in communication, attention, anxiety, depressed mood, labor or work, study, self-control, nausea, headache, and suicidal thoughts<sup>17</sup>. The use of PP-LAI can effectively help MA abusers to abstain from addiction, which is consistent with the report of Soontornniyomkij et al.<sup>18</sup>. This suggests that our results are consistent with previously reported conclusions. Most of the reward effects of drug abuse involve the mesolimbic dopamine system. By activating the ventral tegmental area of the midbrain,

**Table 3.** Neurotransmitter changes before and after treatment.

Neurotransmitter	Control group (n=55)	Study group (n=54)	T value	P value
DA level before treatment	2.44 ± 0.68	2.30 ± 0.70	1.059	0.292
DA level after 6 months of treatment	2.69 ± 0.64	4.57 ± 1.08	11.080	0.000
Gamma-GABA Level before treatment	7.47 ± 2.25	7.35 ± 1.30	0.340	0.734
Gamma-GABA level after 6 months of treatment	7.39 ± 2.43	6.22 ± 1.48	3.029	0.003
5-HT level before treatment	23.78 ± 6.57	24.56 ± 6.78	0.610	0.543
5-HT level after 6 months of treatment	21.94 ± 5.65	18.21 ± 5.06	3.629	0.000

MA enables AD neurons to project to related brain circuits in the limbic system. This process can cause a large amount of DA release, inhibit the activity of monoamine oxidase, and inhibit the degradation of DA. Synaptic gap DA significantly increases, resulting in a rewarding effect and euphoria.

MA withdrawal causes significant emotional distress as the neurobiology involved in addiction are undergoing reductions or cessation in substance. Electroacupuncture promotes the release of different endogenous opioid peptides from the central nervous system, activating both the endogenous opioid  $\mu$  system and dynorphin  $\kappa$  system to suppress withdrawal symptoms<sup>19</sup>; paliperidone palmitate is hydrolyzed to paliperidone in vivo and is a major metabolite of risperidone, which achieves systemic control of psychiatric symptoms mainly through antagonizing central dopamine D2 receptors and serotonin receptors altering neurotransmitter levels<sup>8,20,21</sup>. In this study, we found that after 6 months of treatment, dopamine levels were higher,  $\gamma$ -aminobutyric acid values, and serotonin values were lower in the study group than in the control group. These results suggest that PP-LAI may effectively inhibit hypothalamic and pituitary neurotransmitters and increase dopamine levels by influencing neurotransmitters. In this way, patients' emotions can be effectively stabilized, and finally, their dependence on MA can be effectively alleviated, and MA withdrawal can be assisted. Flack et al.<sup>22</sup> showed that after MA addiction, the value of  $\gamma$ -aminobutyric acid, serotonin, and acetylcholine increased significantly, while the value of dopamine decreased significantly. This is consistent with the conclusion of this study.

However, there are still many defects in this study. First, the number of participants included in this work is small, and subsequent work needs to expand the study cohort to verify the research results in the latest step. In addition, the study lacked a measure of the severity of MA-related psychosis and MA addiction (or methamphetamine use disorder in the DSM-5). We will further refine the results in future studies.

In summary, electroacupuncture combined with long-acting paliperidone palmitate injection can improve withdrawal symptoms in methamphetamine-dependent patients. Modulating neurotransmitter activity can prevent the relapse of withdrawal symptoms in methamphetamine-dependent individuals. We speculate that the therapeutic effect of electroacupuncture may have an impact on patient care. Perhaps electroacupuncture and other acupoint stimulation (acupuncture, massage, etc.) can provide new ideas for comprehensive care of patients.

*Declarations:* ethics approval and consent to participate. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Wuhan

Wudong Hospital (No. WDYYLL202102). Written informed consent was obtained from all participants/local guardians.

*Availability of data and materials:* all data generated or analyzed during this study are included in this published article.

*Competing interests:* all of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

*Funding:* the study is funded by Wuhan Municipal Health Commission Scientific research project (WZ22C36). Funding agencies did not play a role in study design, data collection, analysis and interpretation, and manuscript writing.

*Authors' contributions:* Chen Y, Wei W and Gong J conceived of the study. Qiao J, Wu C and Wang X participated in its design and data collection. Ding Y, Chen H, Lu H, Li M and Ji Q helped with the data analysis and statistics. Li M and Ji Q took part in drafting the manuscript. All authors read and approved the final manuscript.

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