



## Long Term Quality of Life Outcome Among Opiate Addicts After the Nucleus Accumbens Ablative Neurosurgery

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### Abstract

The bilateral Nucleus Accumbens (NAc) ablative neurosurgery has been reported to be a possible treatment to prevent the relapse for the opiate addicts. However, the factors affecting long term quality of life (QoL) outcome of this therapy was not well studied. The cross-sectional study of QoL was conducted on opiate addicts randomly selected from the patients who had undergone the NAc ablative surgery, at their 6th postoperative year by using the WHOQOL-BREF instrument. Opiate addicts who have received detoxification treatment in mandatory residential compulsory rehabilitation centers were randomly selected as comparison samples. The socio-demographic characteristics and the current abstinent status of the participants were obtained by the structured questionnaire, and the Symptom Checklist-90-Revised (SCL-90-R) was applied for assessing the psychological symptoms. Comparing with the opiate addicts who had undergone residential compulsory detoxification, the opiate addicts who had undergone the NAc ablative surgery showed significantly better QoL in all four domains by WHOQOL-BREF instrument. For the surgical individuals, the relapse outcome and the severe psychological symptoms were strongly associated with the worse QoL. Besides severity of psychological symptoms which strongly predict the worse scores in all domains, the multiple linear regression analysis showed: older age, unsatisfied employment status and injection behaviors associated with lower QoL for physical domain; unsatisfied employment and marital status, lower educational level and injection behaviors associated with lower QoL for psychological domain; unsatisfied employment and marital status associated with lower QoL for social domain; unsatisfied employment and marital status, and injection behaviors associated with lower QoL for environmental domains. The results revealed that the opiate addicts represented a better QoL after the NAc ablative neurosurgery, comparing to the ones who received residential compulsory treatment. The relapse outcome and the psychological symptoms play a decisive role on the QoL of the patient long term after the NAc ablative neurosurgery.

**Keywords:** Stereotactic neurosurgery; Nucleus accumbens; Quality of life; Opiate addiction; WHOQOL-BREF; Psychological symptoms

### Introduction

Drug addiction, a chronic relapsing disorders which manifests as compulsive drives to take drugs despite serious adverse sequences, poses great threats to people's health and society's stability [1]. Reports by Chinese government released that registered drug addicts have reached over 2 million until 2013 China [2]. Although lots of attempts have been used to treat opiate addicts, few of the therapies showed satisfying efficacy to prevent the relapse after the detoxification, with the optimal report of abstinent rate being only 15% in 3 years after treatment [3]. As it cannot be helped, majority of opiate addicts who repeatedly relapsed may be placed in mandatory residential compulsory rehabilitation centers for detoxification [3].

Based on the neurophysiological mechanisms underlying the addiction, functional neurosurgeons attempt to apply the stereotactic surgery which makes a mini-invasive lesion in brain structures being of intimate relationships with drug psychological dependence to treat addiction. Gao et al. firstly reported that ablation of the nucleus accumbens (NAc) can effectively alleviate the opiate drug psychological dependence and decrease the relapse rate [4]. One recent large-scale epidemiological investigation in China demonstrated that

abstinent rate of patients undergone the NAc ablative surgery can reach to 50% at fifth postoperative year [5].

For the chronic and relapsing feature of the drug dependence and so various domains of life it may have negative impacts on, much more attention has been given to quality of life (QoL) in the addiction research field [6,7]. An accumulation of studies have indicated that opiate-dependent individuals before any treatments reported a significant lower scores in most domains by health related QoL (HRQoL) instruments compared with general population or a comparison group [8-10]. In addition, several treatments, for example, methadone, naltrexone and buprenorphine substitution treatment showed a positive influence on the opiate addicts, which may be attributed to the abstinence [11-14]. As for the bilateral nucleus accumbens ablative neurosurgery which showed satisfied efficacy to prevent the relapse in long term, Li et al and Ge et al has reported that if abstinence was kept, the five-year postoperative QoL of patients were better than the preoperative conditions [15,16].

Obtaining a better understanding of factors that contributed to high QoL scores, may help the treatment services to make clear how to improve the individuals' QoL [17]. However, previous studies did not assess the predictors of addicts' QoL long term after the bilateral nucleus accumbens ablative neurosurgery [15,16]. Aiming to make clearer how to improve QoL of the opiate-dependent individuals who turned to the NAc targeted neurosurgery for treatment, the influence

of the current status of drug use and psychological symptoms on the patients' QoL were all assessed by the present study on an over one hundred sample at their 6th postoperative year, and other potential predictors including some demographic, psychosocial and drug using-related variables were also analysis for their relationship with the respondents' QoL.

## Methods

### Ethics Statement

The study was examined and approved by the Medical Ethics Committee of Fourth Military Medical University in China, in accordance with the international accepted criteria of research. Though the nucleus accumbens ablation surgery has been stopped as the clinical service in the year 2005 by Chinese government, the researches on surgical treatment for addiction, especially the retrospective studies to evaluate the current status of the patients who have undergone the nucleus accumbens ablation surgery was still strongly supported by the Chinese government, for these studies may supply important data for prompting some more advanced new therapies for treating addiction, e.g. DBS. W

### Samples and participants

The present study was set up as a cross-sectional of study of the current quality of life (QoL) of opiate-dependent individuals who were at their 6th postoperative year after bilateral stereotactical ablation of nucleus accumbens. 272 patients in total have undergone the surgery in the department of neurosurgery of Tangdu Hospital from the year 2000 to 2004, before the time nucleus accumbens ablation surgery has been stopped as the clinical service in the year 2005 by Chinese government. Among them, now the 120 patients were randomly selected to be recruited in the present study by assignment of computerized randomized number, 9 rejected the study and their abstinent status was unknown, 5 patients could not be got in touch by the recorded contact information, 1 patient were confirmed dead with cause unknown, thus totally 105 patients completed the questionnaires. Set as the comparison samples, 150 opiate-dependent individuals who had undergone detoxification in mandatory residential compulsory rehabilitation centers were randomly selected to be involved in the present study, and only 112 opiate-dependent individuals among these group completed the questionnaires.

### Surgical procedure

All the patients have undergone the surgical procedure as following: the patients were placed in a Cosman-Robert-Wells (CRW; Radionics Inc., Burlington, Mass, USA) MRI-compatible head ring with the base ring approximately parallel to the anterior commissure-posterior commissure (AC-PC) line. Then the imaging location was performed by MRI thin-slice scanning. A stereotactic frame-based planning workstation was used. A set of anterior-posterior, lateral, and vertical coordinates was produced for each NAc target. Coordinates of the NAc were as follows: 4.5-6.0 mm below the AC-PC line, 17.5-19.0 mm anterior to the midpoint, 4.5-6.0 mm lateral to the median line. The CRW system coordinates were then entered into the target menu of the CRW program. The CRW system coordinates (AP, lateral and vertical) were acquired and set directly on the CRW. The ablation was performed by the RFG-3CF Radiofrequency Lesion Generator (Radionics, Burlington, MA, USA) with an electrode (1.6 mm in

diameter, 4mm exposed electrode). After stereotactically placing the electrode tip at the target, a low frequency (2Hz) followed by a high frequency (100Hz) stimulus was applied using an amplitude of 6-8V. In addition to hemodynamic and neurologic monitoring, patients were observed by the surgeons and a dedicated nurse for abnormal reactions including fever, diaphoresis, palpitations, headache, dyspnea, dysphasia, paresis, seizure, paresthesia, dysphoria, and akinesia, and a preliminary lesion (45 ,60s) was made. If no abnormal reaction was observed, a definitive radiofrequency lesion (80 ,60s) was carried out, and the lesion procedure was completed when the temperature of electrode tip fall down below the 37 before the electrode was removed from the brain. The CT scan was performed for all patients postoperatively to verify the complete and accurate lesion of the nucleus accumbens.

### Data collection

Data collection was done by veteran investigators who were not informed of the treatment conditions of the participants. All the participants were invited to return to our department, or else the investigators will visit the patients' dwellings (for patients unable to return because of personal reasons), postoperatively at 6 months, 1,3,5 and 6 years, and morphine urinalysis and naloxone test were conducted to confirm the relapsed cases: regardless of any contradictory data, positive morphine urinalysis was considered a relapse; if morphine urinalysis was negative, naloxone testing was performed, positive naloxone testing was also considered a relapse, regardless of other data. In addition, the main reason for reuse of the drugs was surveyed for the relapsed patients. Face to-face interviews was carried out at the last interview at 6 years postoperatively, and the interviews cover respondents' general data, the current status of relapse, the psychological symptoms and focus on the respondents' current QoL.

### Instruments

Information on the socio-demographic characteristics and the current abstinent status of the participants was adopted into the structured questionnaire: age, gender, education, marital status, employment status, etc.

### WHOQOL-BREF instrument

To measure quality of life, we used the World Health Organization Quality of Instrument Abbreviated (WHOQOL-BREF), which contains 26 items and four domains: physical, psychological, social and environmental domains [18]. The four domain scores denote an individual's perception of quality of life in each particular domain. The mean score of items within each domain is used to calculate the domain scores according to the manual. Domain scores are scaled in a positive direction, scaled from 0-100, with higher scores indicate higher quality of life. In addition, two items from the Overall quality of Life and General Health facet have been included. Validity and reliability of WHOQOL-BREF has been verified by several studies [19], including ones performed on Chinese population [20,21].

### Self-reporting inventory

Psychological symptoms were assessed by Symptom Checklist-90-Revised (SCL-90-R), a 90-item self-report measure of global psychopathological symptoms. The Chinese version of the SCL-90 has a good reliability, indicated by a Cronbach's alpha of 0.97 [22]. The

instrument measures recent psychological complaints (past 7 days) on 10 subscales: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and additional. Symptoms are rated on a 5-point Likert scale ranging from "1. Not at all" to "5. Extremely", with higher scores indicating more severe complaints. Scores were generated for nine symptom subscales and an overall Global Severity Index (GSI). The positive symptom distress index (PSDI) measuring the intensity of symptoms, and the positive symptom total (PST) representing the number of items indicating psychological symptoms, were calculated as well.

### Statistical analysis

SPSS17.0 was used for all analyses in the present study. Descriptive statistics was used to assess the socio-demographic and the current relapse characteristics of the participants, and the difference of these characteristics between the participants undergone the NAc ablative surgery (NAc surgical group) and the ones undergone the detoxification in compulsory rehabilitation centers (Compulsory detoxification group) were examined using  $\chi^2$  test. We compared the WHOQOL-BREF subscale scores between the participants of NAc surgical group and compulsory detoxification group, and between the relapsed participants and the abstained ones of the NAc surgical group, by using the independent-sample t-test. Pearson correlation analysis was used to analyze the relationships between the each of the QoL domain scores and each of the psychological symptom scores for the total patients who had undergone the surgery, and between the potential predictors and each of the QoL domain scores for the relapse patients. To investigate the independent contribution of individual predictors to QoL, multiple linear regression procedure applying a stepwise search way, was used to assess the effect of each of the independent variables on each of WHOQOL-BREF domain score. All statistical inferences were based on a significance level of P (two-sided) <0.05.

### Results

#### Study sample characteristics

Table 1 describes sample characteristics. The opiate addicts have regularly consumed drugs for 116.83 ± 41.54 months on average before the surgical treatment, with the mean daily dosage of 1.14 ± 0.74g. There were no significant difference between the studied patients undergone the surgery and the comparison samples of participants who have undergone the detoxification in mandatory residential compulsory rehabilitation centers, with respect to age, education level, marital status, employment and type, duration, method of administration or quantity of drug abuse (P<0.05) before treatment, which were shown in Table 1. Among the 63 patients who have frequent injection behaviors before the surgery, 5, 41 and 25 ones have been infected by HIV, HBV and HCV respectively. While for the rest of patients who hardly use drugs by injection, only 6 and 2 patients were HBV and HCV positive respectively.

		detoxification (n=112)
Socio-demographic characteristics		
Age, mean (SD),y	36.87 ± 5.33	36.38 ± 6.99
Male	101 (96.2)	99 (88.4)**
Education		
Elementary school	49 (46.7)	58 (51.8)
High school	42 (40.0)	46 (41.1)
Superior to special course	14 (13.3)	8 (7.1)
Marital status		
Unmarried	24 (22.9)	32 (28.6)
Married	52 (49.5)	49 (43.8)
Divorced/widowed	29 (27.6)	31 (27.7)
Employment		
Employed (high paid)	12 (11.4)	8 (7.1)
Employed (low paid)	63 (60.0)	60 (53.6)
Unemployed	30 (28.6)	44 (39.3)
Drug use characteristics Before treatment		
Drug type		
Heroin	78 (74.3)	87 (77.7)
Non-heroin opiates	27 (25.7)	25 (22.3)
Months of regular use#, mean(SD),y	116.83 ± 41.54	113.10 ± 59.31
Average daily dosage, mean(SD),g/day	1.14 ± 0.74	1.05 ± 0.72
Frequent injection behaviour	63 (60.0)	68 (60.7)
After treatment (only for relapsed patients underwent surgery, n=41)		
Drug type		
Herion	25 (61.0)	
Non-heroin opiates	14 (34.1)	
New type drugs	2 (4.9)	
Abstinent periods, mean(SD),m	12.15 ± 12.32	
Average daily dosage, mean(SD), g/day	1.13 ± 0.95	
Average daily frequency, mean(SD),/day	2.90 ± 1.56	
Frequent injection behaviour	24 (58.5)	
*Data are presented as number (percentage) unless otherwise indicated. **Females are too less for both two groups to test the sex constitution difference. #Regular use means at least weekly use.		

**Table 1:** Socio-demographic and drug use characteristics by treatment condition\*

	NAc ablative surgery (n=105)	Residential compulsory

## Opiates relapse and abstinence

Of all participants who have undergone the bilateral NAc ablative surgery for treating opiates dependence, 64 patients were confirmed to be persistently abstinent from the opiates or other kind of addictive drugs until interviewed, accounting for 53.3% of the total patients randomly selected, 39 patients have used opiates again, 2 turned to another kind of new type drugs, i.e. methamphetamine, thus totally 41 patients were took as the relapsed participants. As seen in table 1, According to their self-reports, the mean daily dosage of drugs used by the participants after relapse was  $1.13 \pm 0.95$  g, with the mean daily drug using frequency of  $2.90 \pm 1.56$  times, and 58.5% of them still reported frequent injection behaviors currently. In addition, NAc ablation also affects some other type of addiction for patients. For 34 patients who have alcoholic addiction (average alcoholic daily intake > 500g) before surgery, 27 patients significantly reduced their alcoholic daily intake (<50 g) postoperatively. There were also only 3 patients showed changes on sexual desire, among which 2 patient reported hyposexuality and 1 patient reported hypersexuality.

All the relapsed patients gave the main reason for reused of drugs, for the most to the least are lack of family and social support (for 17 patients), unable to get away from the drug related people or environment (for 12 patients), and negative life events (for 9 patients), only 2 and 1 patients relapsed because of physiological symptoms and residual psychological dependence for drugs respectively.

## Current quality of life(QoL)

Opiate dependence individuals who had undergone the NAc ablative neurosurgery appeared most satisfied when interviewed with the domain "physical", with the mean scores of 62.76 (Table 2), and 76.2% of the respondents reported scores over 50. While for the domain "psychological", the participants seemed to be of least satisfaction, which had the lowest mean scores of 51.15, and only 53.3% the respondents reported scores over 50. The respondents reporting more than 50 scores on the "social" and "environmental" domains took different portions of total, with the moderate mean score of 58.97 and 56.55, respectively.

Domain	Mean score $\pm$ SD		df	P value
	NAc ablative surgery (n=105)	Residential compulsory detoxification (n=112)		
Physical	62.76 $\pm$ 17.81	52.43 $\pm$ 17.52	215	<0.001**
Psychological	51.15 $\pm$ 18.90	44.56 $\pm$ 16.85	215	0.007**
Social	58.97 $\pm$ 19.33	44.23 $\pm$ 18.59	215	<0.001**
Environmental	56.55 $\pm$ 15.97	34.94 $\pm$ 14.76	215	<0.001**
Global	55.36 $\pm$ 19.98	41.52 $\pm$ 18.09	215	<0.001**

\*\*P<0.01.

**Table 2 :** WHOQOL-BREF scores by treatment condition.

In comparison, the QoL of addicts undergone the residential compulsory detoxification showed significantly lower scores than the addicts treated by NAc-targeting surgery in all four domains, i.e. "physical", "psychological", "social" and "environmental", as well as global quality of life (Table 2).

The QoL of total addicts undergone the NAc ablative surgery showed significant lower scores than the normal Chinese population (n=777)[23] in the "physical" ( $62.67 \pm 17.81$  vs  $69.38 \pm 10.57$ ) and "psychological" ( $51.15 \pm 18.90$  vs  $58.81 \pm 8.41$ ) domain (P<0.05), but represented no significant difference in the "social" ( $58.97 \pm 19.33$  vs  $60.06 \pm 8.89$ ) and "environmental" ( $56.55 \pm 15.97$  vs  $55.63 \pm 9.56$ ) domain (P>0.05). In addition, the abstinent patients showed equal scores to the normal Chinese population in "physical" ( $68.47 \pm 16.39$  vs  $69.38 \pm 10.57$ ) and "psychological" ( $57.49 \pm 17.94$  vs  $58.81 \pm 8.41$ ) domain (P>0.05), and showed even higher scores in in the "social" ( $65.89 \pm 16.04$  vs  $60.06 \pm 8.89$ ) and "environmental" ( $61.23 \pm 13.36$  vs  $55.63 \pm 9.56$ ) domain (P<0.05).

## Impact of current opiate use and psychological symptoms on QoL

According to the current status of opiates use, the samples undergone the NAc ablative surgery were split up into two subgroups (Table 3). The comparison of the QoL demonstrated that relapsed patients had significantly lower scores than the ones who were still abstinent from the opiates when interviewed, in all four domains and global score by the scaling of WHOQOL-BREF instruments. The relapsed patients undergone the surgery still showed better global score than the compulsive detoxified addicts (P=0.098), because of significantly higher score in "environmental" domain (P<0.001). However, the surgical relapsed patients represented scores equal to the compulsive detoxified addicts in "physical" (P=0.657), "psychological" (P=0.279) and "social" (P=0.252) domains. On the other hand, the surgical abstinent patients showed significantly higher scores in all four domains and global score than the compulsive detoxified addicts (P<0.001).

	Mean score $\pm$ SD		df	P value
	Abstinent (n=64)	Relapsed (n=41)		
WHOQOL-BREF scores				
Physical	68.47 $\pm$ 16.39	53.83 $\pm$ 16.37	103	<0.001**
Psychological	57.49 $\pm$ 17.94	41.26 $\pm$ 16.02	103	<0.001**
Social	65.89 $\pm$ 16.04	48.17 $\pm$ 19.23	103	<0.001**
Environmental	61.23 $\pm$ 13.36	49.24 $\pm$ 17.08	103	<0.001**
Global	60.55 $\pm$ 17.57	47.26 $\pm$ 21.01	103	0.001**
SCL-90 scores				
GSI	1.52 $\pm$ 0.47	1.96 $\pm$ 0.74	103	0.001**
PST	29.59 $\pm$ 19.45	43.10 $\pm$ 24.22	103	0.002**
PSDI	2.39 $\pm$ 0.53	2.85 $\pm$ 0.68	103	<0.001**
So	1.34 $\pm$ 0.52	1.80 $\pm$ 0.86	103	0.003**
Oc	1.79 $\pm$ 0.66	2.22 $\pm$ 0.97	103	0.003**
Is	1.62 $\pm$ 0.52	1.96 $\pm$ 0.82	103	0.022*
De	1.59 $\pm$ 0.58	2.22 $\pm$ 0.97	103	<0.001**
An	1.39 $\pm$ 0.51	1.82 $\pm$ 0.82	103	0.004**
Ho	1.70 $\pm$ 0.76	2.26 $\pm$ 1.01	103	0.003**



Pa	1.23 ± 0.36	1.44 ± 0.55	103	0.042*
Pi	1.53 ± 0.58	1.96 ± 0.99	103	0.015*
Ps	1.42 ± 0.43	1.79 ± 0.78	103	0.006**
Ad	1.67 ± 0.70	2.02 ± 0.81	103	0.018*

\*\*P<0.01;\*P<0.05;GSI: Global Severity Index; PST: Positive Syndrome Total; PSDI: Positive Symptom Distress Index. Subscores on 10 dimensions: So: Somatization; Oc: Obsessive Compulsive; Is: Interpersonal Sensitivity; De: Depression; An: Anxiety; Ho: Hostility; Pa: Phobia Anxiety; Pi: Paranoid Ideation; Ps: Psychoticism; Ad: Additional items.

**Table 3:** QoL and SCL-90scores of surgical participants by abstinent status.

Similarly, for the patients who have undergone the surgery, relapsed ones also scored significantly lower than the abstinent ones in all subscales by the SCL-90 scales (Table 3).To probe the relations of quality of life and psychological symptoms of the patients, the correlation coefficients between subscores evaluated by the WHOQOL-BREF and SCL-90-R were calculated (Table 4). It can be found that Global score and subscores of all four domains by WHOQOL-BREF were significantly and negatively correlated with each of the nine symptom dimension scores of the SCL-90-R (P < 0.05).

	Physical		Psychological		Social		Environmental	
	r	P Value	r	P Value	r	P Value	r	P Value
GSI	-0.60 5	<0.001* *	-0.68 0	<0.001* *	-0.662	<0.001* *	-0.646	<0.001* *
PST	-0.58 4	<0.001* *	-0.65 3	<0.001* *	-0.591	<0.001* *	-0.584	<0.001* *
PSDI	-0.52 7	<0.001* *	-0.60 8	<0.001* *	-0.489	<0.001* *	-0.572	<0.001* *
So	-0.48 5	<0.001* *	-0.47 7	<0.001* *	-0.526	<0.001* *	-0.513	<0.001* *
Oc	-0.58 7	<0.001* *	-0.65 3	<0.001* *	-0.589	<0.001* *	-0.582	<0.001* *
Is	-0.52 4	<0.001* *	-0.60 3	<0.001* *	-0.547	<0.001* *	-0.503	<0.001* *
De	-0.61 2	<0.001* *	-0.72 4	<0.001* *	-0.699	<0.001* *	-0.640	<0.001* *
An	-0.52 3	<0.001* *	-0.58 9	<0.001* *	-0.629	<0.001* *	-0.587	<0.001* *
Ho	-0.42 9	<0.001* *	-0.55 9	<0.001* *	-0.503	<0.001* *	-0.533	<0.001* *
Pa	-0.50 5	<0.001* *	-0.53 1	<0.001* *	-0.591	<0.001* *	-0.597	<0.001* *
Pi	-0.54 5	<0.001* *	-0.59 7	<0.001* *	-0.609	<0.001* *	-0.626	<0.001* *
Ps	-0.46 7	<0.001* *	-0.56 5	<0.001* *	-0.531	<0.001* *	-0.545	<0.001* *

Ad	-0.58 7	<0.001* *	-0.60 6	<0.001* *	-0.538	<0.001* *	-0.555	<0.001* *
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**Table 4:** Correlation analysis between HRQOL and psychological symptoms for patients undergone NAC ablative surgery.

### Determinants of QoL

Multiple regression analysis was applied to find the possible determinants of QoL for all the opiate-dependent individuals who have undergone the NAC ablative neurosurgery. The final models by stepwise regression for all the four domains' scores were showed in the Table 5. The GSI, which indicates the severity of the psychological symptoms, represented to be the strong negative predictors of all four domains' scores by WHOQOL-BREF instruments. In addition, the final regression model for "physical" domain contains another 3 predictor variables including age, employment status and injection behaviors: older age and injection behaviors were significantly associated with the lower score, and worse employment status strongly predicted lower score; the final regression model for "psychological" domain contains another 4 predictor variables including employment and marital status, education level and injection behaviors: education level was significantly and negatively associated with the score, worse employment and marital status and injection behaviors strongly predicted lower score; the final regression model for "social" domain contains only 2 predictor variables except for GSI, i.e. employment and marital status, both of which were significantly and negatively associated with the score; and the final regression model for "environmental" domain contains another 3 predictor variables including employment and marital status, and injection behaviors: worse employment and marital status and injection behaviors all strongly predicted lower score. The four models can explained 53.8%, 64.6%, 53.8% and 54.8% of the variance of scores in the domains "physical", "psychological", "social" and "environmental" respectively.

Remaining predictors	B	SE	Beta	t	P
<b>Physical<sup>a</sup></b>					
(constant)	117.86 7	9.006		13.087	<0.001**
Age	-0.584	0.241	-0.175	-2.428	0.017*
<b>Employment status</b>					
Unemployed	-19.818	4.470	-0.505	-4.434	<0.001**
Employed (low paid)	-9.148	3.840	-0.253	-2.383	0.019*
Employed (high paid)	0 [Reference]				NA
<b>Injection behaviour</b>					
Frequent injection behaviour	-6.666	2.450	-0.184	-2.721	0.008**
No injection behaviour	0 [Reference]				NA
Global Severity Index	-10.895	2.143	-0.383	-5.083	<0.001**
<b>Psychological<sup>b</sup></b>					
(constant)	96.624	5.587		16.579	<0.001**
<b>Employment status</b>					

Unemployed	-17.792	4.292	-0.427	-4.145	<0.001**
Employed (low paid)	-8.733	3.790	-0.227	-2.304	0.023*
Employed (high paid)	0 [Reference]			NA	
Marital status					
Unmarried	-0.787	3.164	-0.018	-0.249	0.804
Married	8.588	2.735	0.228	3.140	0.002**
Divorced/widowed	0 [Reference]			NA	
Educational level					
Elementary school	-9.840	3.674	-0.261	-2.678	0.009**
High school	-8.888	3.617	-0.232	-2.457	0.016*
Superior to special course	0 [Reference]			NA	
Injection behaviour					
Frequent injection behaviour	-4.945	2.302	-0.129	-2.148	0.034*
No injection behaviour	0 [Reference]			NA	
Global Severity Index	-14.258	2.023	-0.472	-7.049	<0.001**
Social c					
(constant)	89.508	6.028		14.850	<0.001**
Employment status					
Unemployed	-15.405	4.836	-0.362	-3.186	0.002**
Employed (low paid)	-8.511	4.256	-0.217	-0.200	0.048*
Employed (high paid)	0 [Reference]			NA	
Marital status					
Unmarried	2.833	3.686	0.062	0.769	0.444
Married	10.688	3.178	0.278	3.363	0.001**
Divorced/widowed	0 [Reference]			NA	
Global Severity Index	-15.951	2.303	-0.517	-6.925	<0.001**
Environmental d					
(constant)	80.160	4.958		16.168	<0.001**
Employment status					
Unemployed	-8.927	3.957	-0.254	-2.256	0.026*
Employed (low paid)	-4.081	3.480	-0.126	-1.173	0.244
Employed (high paid)	0 [Reference]			NA	
Marital status					
Unmarried	3.675	3.010	0.097	1.221	0.225
Married	10.838	2.604	0.341	4.162	<0.001**
Divorced/widowed	0 [Reference]			NA	
Injection behaviour					

Frequent injection behaviour	-6.817	2.177	-0.210	-3.132	0.002**
No injection behaviour	0 [Reference]			NA	
Global Severity Index	-12.260	1.896	-0.481	-6.465	<0.001**
#The analysis only includes patients who have undergone Nucleus accumbens ablative surgery.					
**Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed). Frequent injection behavior: at least 2 times of injection behavior per day.					
a R <sup>2</sup> =0.560, adjusted R <sup>2</sup> =0.538, P<0.001**; b R <sup>2</sup> =0.673, adjusted R <sup>2</sup> =0.646, P<0.001**; c R <sup>2</sup> =0.560, adjusted R <sup>2</sup> =0.538, P<0.001**; d R <sup>2</sup> =0.574, adjusted R <sup>2</sup> =0.548, P<0.001**.					

**Table 5:** Final model of the linear multivariate regression analysis including significant predictors of different WHOQOL-BREF subscores#

For the 41 relapsed opiate-dependent individuals who had undergone the NAc ablative surgery, the association between the drug-reuse related characteristic and the WHOQOL-BREF scores was also studied by correlation analysis, showed in Table 6. Type of the relapsed drugs showed no clear relationship with scores of any domains. Longer abstinent periods were only significantly correlated with the higher score in “psychological” domain. Both average daily dosage and daily frequency of the drug reuse after the relapse were significantly and negatively correlated just with the score in “environmental” domain. Similar to the total samples, the injection behaviors were still significantly associated with the worse scores in the “physical”, “psychological”, and “environmental” domains.

	Physical		Psychological		Social		Environmental	
	r	P Value	r	P Value	r	P Value	r	P Value
Drug type	0.035	0.828	-0.073	0.649	-0.033	0.837	-0.138	0.390
Abstinent periods	0.302	0.055	0.393	0.011*	0.240	0.130	0.255	0.108
Average daily dosage	-0.183	0.252	-0.257	0.105	-0.206	0.197	-0.310	0.049*
Average daily frequency	-0.257	0.104	-0.293	0.063	-0.235	0.139	-0.319	0.042*
Frequent injection behaviour	-0.413	0.007*	-0.321	0.040*	-0.277	0.080	-0.377	0.015*

**Table 6:** Correlation analysis between WHOQOL-BREF and drug reuse characteristics for relapsed patients undergone NAc ablative surgery.

## Discussion

Focusing on respondents' reported satisfaction with life as a whole, quality of life constructs a multifaceted aspect of well-being directly

influencing the daily activity and social functions, and thus represents an important measure to assess outcome of certain medical interventions [24]. The present study firstly study the current QoL of patients who had undergone the bilateral NAc ablative surgery for treating opiate dependence, by using the generic QoL instrument WHOQOL-BREF which are being applied by more QoL assessments. Our results not only showed the bilateral NAc ablative surgery can effectively decrease the relapse rate in the long term, but also indicated its positive effects on the QoL of the opiate dependents, making the surgical therapy targeted at NAc deserve more attention for treating opiate addiction in future. And among the four domains, the addicts scored highest in "physical" and lowest in "psychological", indicating the surgery showed impact of viable power on different aspects of the QoL, i.e the physical well-beings most significantly improved and there is still a lot of measures to take for obtaining more psychological satisfaction.

It has been well established that opiate abuse can significantly worsen the addicts' QoL [8-10], and several studies have confirmed the impact of current heroin use to be decisive for the improvement of OoL of opiate-dependent individuals after the treatment such as MMT, thus successful abstinence from drugs in the long periods should be a key factor to make the addicts' QoL better [12,25,26]. Our study by comparing the QoL between the patients who had relapsed and not get the similar results, again testify the abstinent status to be important for the improvement of patients' OoL after the treatment. It can be inferred that only the persistent abstinence from the drugs assured the patients' QoL of sustainable improvement after the surgery.

Psychological symptoms has been reported to be strong factor associating with the low QoL by studies on different samples [27,28], and various studies have indicated that low QoL of opiate-dependent individuals can be partly explained by the high prevalence of psychological co-morbidity [29,30]. Previous studies on QoL of opiate-dependent individuals have reported lower QoL scores among persons with co-occurring psychiatric problems when compared with individuals without psychiatric co-morbidity [24]. The study assessing the QoL outcome of certain opiate dependence treatment, such as MMT, also indicates the persons with an overall psychopathology scored significantly lower than ones with no psychopathology in all domains by QoL instrument after a period of treatment [26]. Our study revealed the similar results that psychological symptoms contributed a lot to the worse QoL of opiate addicts after the surgery, for GSI scores by SCL-90 can explain over 40% variability of the scores in all four domains of WHOQOL-BREF instrument, showing the psychopathology can not only impair the addicts' physical and psychological status, but also negatively influenced their social functions and environmental satisfaction. It can also be observed that among all the dimensions of psychological symptoms, depression may contribute most to the negative well-being in all domains. Therefore, it would be much more appropriate to develop integrated mental health, especially by intervening the depression, as the standard of care for the opiate dependence individuals after the addiction treating neurosurgery.

By applying the multivariate design, various socio-demographic and drug-related factors were explored whether to be the determinants of the QoL for addicts 6 years after the NAc ablative surgery. Though some previous studies have launched the similar works [24], our multivariate analysis firstly went by WHOQOL-BREF instruments. Our results indicated the drug use history including regular use time,

average daily dosage and drug type all have no clear relationship with the participants' current QoL, which has been confirmed by several previous studies [8,26,31,32], thus if the surgery effectively enabled the patients to be abstinent, the improvement of QoL will not be influenced by the patients' previous addiction severity. However, the injection behavior history before surgery seemed to show a long term impact on the patients' QoL, and it is strongly associated with the low scores in "physical", "psychological" and "environmental" domains. This result may be explained by the high vulnerability to be infected by HIV, HBV or HCV, for the injection behaviors during drug abuse have been the main transmission approach for these infectious diseases in China [33]. Actually, our survey has represented high incidence of HIV, HBV and HCV for the patients who have frequent injection behaviors than the ones who did not. Suffering from these diseases will impair the patients' physical health, and also bring lots of negative influence on the aspect of psychological condition and social functions. Many studies have showed physical and mental (HR)QoL are lower among persons living with HIV infection [34], and HBV and HCV were also reported to impair the patients (HR)QoL [35,36].

By the present study, employment and marital status seemed to play strong impact on the current QoL of opiate-dependent individuals from multifaceted aspects long term after the NAc ablative neurosurgery. The definition of employment status in the present study not only indicated whether to be regular employed, but also labeled the level of opiate-dependent individuals' financial input. Enhancement of social inclusion was observed by several studies to have a positive impact on the individuals' QoL [37]. Having good friends and structured daily activities were also confirmed to be strong determinants for the better QoL of addicts after the treatment [26]. Actually, these positive contributors all mainly depend on the assumption of stable employment. Meanwhile, the poorly paid job always means the worse working environment. Thus, it is not difficult to understand why the employment status determined the scores of all the four domains of the WHOQOL-BREF instruments. Additionally, marital status also contributed to the QoL scores in "psychological", "social" and "environmental" domains. In China, most opiate-dependent individuals will live lonely once they get divorced or widowed or they still could not find partner, and loneliness have been confirmed to be a strong negative contributor to the individuals' QoL by many previous studies [26].

Our study also analyzed the influence of the drug-reuse related factors on the QoL of the 41 relapsed opiate dependence individuals 6 years after the NAc ablative neurosurgery by using the correlation analysis. The results showed that the relapsed drug type has no clear relationships with the QoL, in spite that some patients have reused the new type of drugs such as methamphetamine. The earlier abstinent time only contributed to the worse "psychological" conditions, for the longer period of drug reuse will cause longer period of support lost from family and society, as well as more financial burdens by the drugs assumption. The current drug daily dosage and frequency contributed a lot to the "environmental" well-being, which may be explained by the fact that addicts who use drugs more frequently will be exposed to the worse living and social surroundings, and the current drug daily dosage and frequency were highly correlated. Therefore, in order to improve the relapsed opiate independent individuals' QoL after the surgery, preventing the relapse or decreasing the drug use frequency if relapse may be the limited measures.

Ultimately, this study showed that except for preventing relapse, there is still a lot of need to do with the opiate-dependent individuals

on various life domains, especially by intervening the addicts' psychological symptoms to improve their QoL in long term after the bilateral NAc ablative neurosurgery for treating opiate addiction. Actually, with the rapid development of stereotactic and functional neurosurgery, much advanced techniques such as deep brain stimulation which targets the NAc will be applied for the treatment of opiate dependence, for the occurrence of adverse events has made the brain nucleus ablative surgery to be the history [16,38]. Consequently, a more comprehensive approach, which goes beyond the medical care and surgical strategy, including specific attention for psychological complaints and support in family, occupational and social inclusion issues, should be recommended for surgical treatment for opiate dependence generally in future.

### Limitations

Some limitations of the present study should be taken into account. Firstly, for the lack of enough preoperative data, our study may not accurately describe the effect of surgery on addicts' QoL. Secondly, the analyses included patients undergone compulsory detoxification as a comparison group, a stronger comparison would have involved patients following both compulsory detoxification and surgical treatment over 6-years. Thirdly, the use of step-wise multiple regressions could capitalize on specific characteristics of the sample, such that study results warrant replication. Fourthly, because the study was the cross-sectional design, the causality could not be examined, and future longitudinal research was needed. Finally, 50~60% of the variance of total scores in all four domains can be explained by our regression model, indicating there are other factors not included will have impact on the addicts' QoL.

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