

Time and risk factors associated with relapse among drug-dependent patients who underwent neurosurgery by ablating the nucleus accumbens

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The aim of the present study was to examine the relapse time and analyse the social, psychological and physical factors related to relapse among drug-dependent patients who had undergone neurosurgery by ablating the nucleus accumbens (NAc surgical group) and those who had undergone detoxification with non-operative treatment in residential compulsory rehabilitation centres (control group). A total of 100 patients from the NAc surgical group and 92 patients from the control group were recruited in the study for 5 years. Information regarding their experiences of previous abstinence from drug use and the relapse time was obtained by interviews, while the relapse reasons were obtained through questionnaire. The study shows that there is a significant correlation in relapse reasons between the two groups. 'Relief from disturbance' (psychological factor) and 'peer influence' (social factor) were the two main factors associated with relapse. Factors like 'desire for last use' and 'boredom' (psychological factor) were more associated with relapse in the control group than the NAc surgical group. At 5 years post-operation, the number of patients in the employment and married status in non-relapse group was significantly higher than in the relapse group. There was also a statistical difference in the 5-year survival rate between them. The average relapse time was the first three years. Thus prevention of relapse to drug dependence after detoxification, especially for those with NAc surgery should be improved to focus on the main factors and time.

Keywords: Drug dependence, neurosurgery, nucleus accumbens, relapse.

DRUG dependence, especially opioid dependence, is a chronic and serious brain disorder with a high tendency

of relapse¹. Although many studies were aimed to solve the problems of drug dependence, the success rate of treatment was as low as 3–7% (ref. 2). Based on the significant function of the nucleus accumbens (NAc) in the mesocorticolimbic pathway and its important role in drug dependence^{3,4}, the Department of Neurosurgery of Tangdu Hospital in China has been treating drug dependence by ablating the bilateral NAc with stereotactic surgery since July 2000. In a 15-month follow-up, Gao *et al.*⁵ reported that the NAc lesion by stereotactic surgery could effectively alleviate the drug psychological dependence and improve the non-relapse rate. Although the results of relapse prevention by the NAc surgery are somewhat satisfactory, few studies have been done to examine the factors associated with relapse for unsatisfactory results after the NAc surgery.

In the clinical literature, various related factors such as peer-group influence, poor family and social support, negative mood and stressful life events are well known to be associated with relapse after traditional therapy⁶. The intrapersonal factors (i.e. negative emotions, physical discomfort, urge and temptation) and interpersonal factors (i.e. conflict with others, social pressure, pressure times) have been identified as the two main high-risk factors⁷.

Because a better knowledge of related factors with relapse may aid in finding ways for improving the abstinence rate, it is of major clinical importance to understand the average relapse time and the main factors that contribute to relapse after the NAc surgery. The aims of this study were to examine the relapse time and etiology of patients after surgery by ablating the NAc to alleviate drug dependence.

We conducted a follow-up study with 100 patients as a sample for the long-term outcomes of surgery by ablating the NAc at the end of 2009. Hundred patients were randomly selected from a total of 272 who had undergone the neurosurgery by ablating the NAc before November 2004 at Tangdu Hospital. The follow-up study was performed by face-to-face interview and examination. The evaluation was done by two trained neuropsychologists. In this study, drug-dependent patients undergoing detoxification by the method of pharmacotherapy and psychotherapy in residential compulsory rehabilitation centres in Xi'an were chosen as control subjects. Details of the neurosurgery by ablating the NAc are given elsewhere⁸.

The study protocol was examined and approved by the Ethics Committee of the Fourth Military Medical University in China and adhered to the tenets of the Declaration of Helsinki. All the subjects and guardians, if any, were informed in detail about the nature and duration of the study, as well as the risks and benefits of the proposed treatment. Each participant gave written informed consent to participate in the study.

The non-relapse rate was confirmed by morphine urine test and naloxone provocative test to decrease the false

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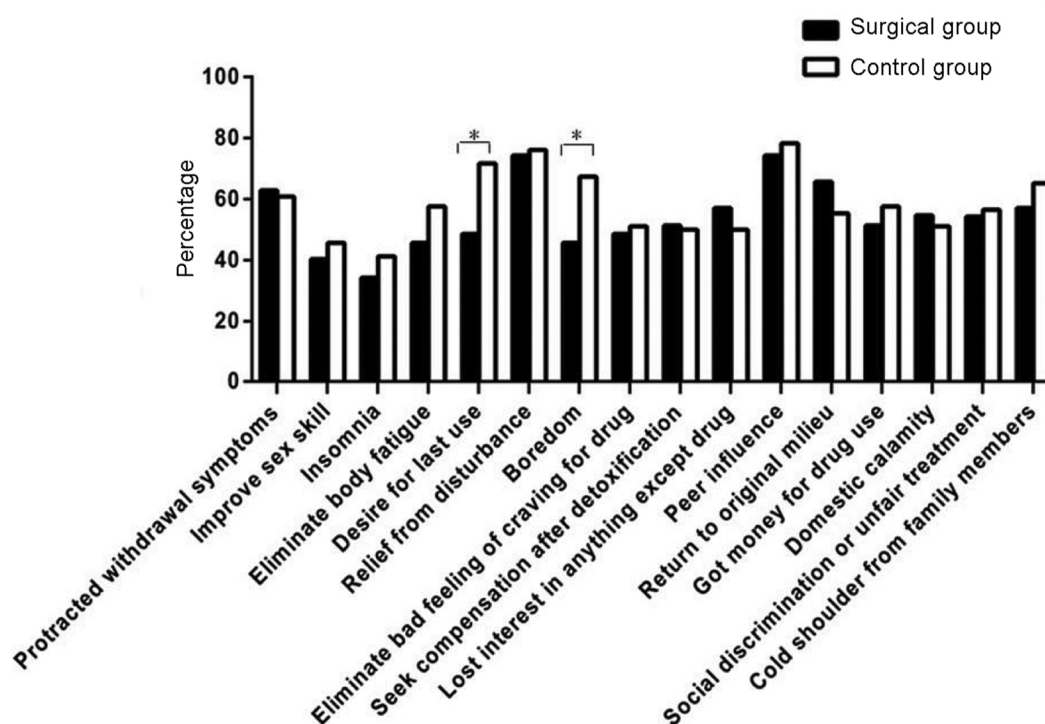


Figure 1. Range of RFDA-16 items by percentage of patients in the surgical and control groups. Comparison of percentage of patients in each RFDA-16 item between the NAc surgical group and the control group (* $P < 0.05$).

positive and negative rates. For each relapsed patient, 16-items relapse factors of drug addiction (RFDA-16) questionnaire was used to obtain the relapse reasons. The RFDA-16 questionnaire was developed by the Chinese National Institute on Drug Dependence. It indicates that the item is concordant with an individual's reasons to relapse. It is comprised of three factors: physical (four items), psychological (six items), social factors (six items). There were 16 items for relapsed patients to answer with yes/no. At last, the percentage of patients who answered yes for each item was analysed. The reliability and validity of the RFDA-16 questionnaire have been assessed by several studies about relapse in China⁹.

Descriptive statistics was used to assess the socio-demographic characteristics, relapse time and reasons. The percentage of patients in each RFDA-16 item was compared between the NAc surgical and control groups using chi-square test. Distribution of patients by category of marital status, employment, education level and occurrence of adverse events was compared between non-relapse and relapse groups with NAc surgery using chi-square test. The Spearman correlation was also performed between the two groups. Survival curves were compared using the log-rank test. All analyses were conducted using SPSS for Windows. A value of $P < 0.05$ was accepted as statistically significant.

Ninety three out of hundred patients with surgery were willing to participate in the study, whereas seven patients

refused or were lost to follow-up. There were 58 non-relapsed and 35 relapsed patients. The 5-year non-relapse rate was 58% if the lost cases were considered as relapse. In the control group, all 92 patients from residential compulsory rehabilitation centres in Xi'an relapsed in 5 years, and the non-relapse rate was 0% for 5 years.

There were no significant differences between the NAc surgical group and control group with respect to age, education level, marital status, employment, abuse duration, method of administration, or quantity of drug abuse ($P > 0.05$) before treatment. Details of the patients are available elsewhere⁸.

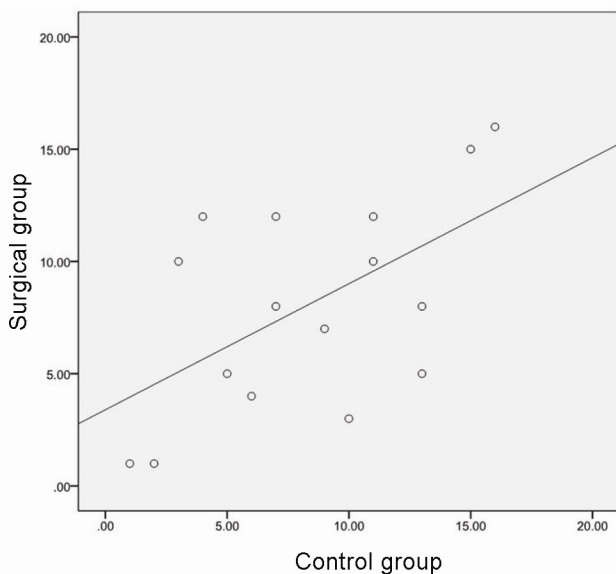
In the NAc surgical group, 'protracted syndromes' (62.9%) and 'eliminate body fatigue' (45.7%) were the main physical factors for relapse; 'relief from disturbance' (74.3%) and 'lost interest in anything except drug' (57.1%) were the main psychological factors, while 'peer influence' (74.3%) and 'returning to original milieu' (65.7%) were the main social factors for relapse (Figure 1).

In contrast, in the control group, 'protracted Syndrome' (60.9%) and 'eliminate body fatigue' (57.6%) were the main physical factors for relapse: 'relief from disturbance' (76.1%) and 'desire for last use' (71.7%) were the main psychological factors, while 'peer influence' (78.3%) and 'cold shoulder from family members' (65.7%) were the main social factors for relapse.

With the chi-square test, there were significant differences in the percentage of patients for the psychological

Table 1. Range of RFDA-16 items by percentage of patients in the surgical and control groups

Factors	Rank		$R = 0.528, P = 0.036$
	Surgical group ($n = 35$)	Control group ($n = 92$)	
Physical factors			
Protracted withdrawal symptoms	4	6	
Improve sex skill	15	15	
Insomnia	16	16	
Eliminate body fatigue	12	7	
Psychological factors			
Desire for last use	10	3	
Relief from disturbance	1	2	
Boredom	12	4	
Eliminate bad feeling of craving for drug	10	11	
Seek compensation after detoxification	8	13	
Lost interest in anything except drug	5	13	
Social factors			
Peer influence	1	1	
Return to original milieu	3	10	
Got money for drug use	8	7	
Domestic calamity	12	11	
Social discrimination or unfair treatment	7	9	
Cold shoulder from family members	5	5	

**Figure 2.** Correlation of the relapse reasons between the surgical and the control groups ($P < 0.05$).

factors ('desire for last use' - $\chi^2 = 6.010, P = 0.014$ and 'boredom' - $\chi^2 = 5.028, P = 0.025$) (Figure 1).

Correlation of the relapse reasons was found between the NAc surgical group and the control group by Spearman assay (Table 1 and Figure 2). The rank correlation coefficient was 0.528 and $P = 0.036$.

There was no significant difference in the education level between relapse and non-relapse patients (Table 2; $\chi^2 = 4.324, P = 0.115$). The number of married people among the non-relapse patients was significantly higher than that for the relapse patients (Table 3; $\chi^2 = 13.501,$

$P = 0.001$). At 5 years post-operation, statistical analysis showed that there was significant difference between the relapse and non-relapse patients with respect to employment status, with the employment included the high paid and low paid (17.1% + 37.1% = 54.3%, 13.8% + 74.1% = 87.9%) (Table 4; $\chi^2 = 15.115, P = 0.001$).

Information about adverse events was obtained from the patients themselves (Table 5). A total of 90 persistent adverse events were reported in 51 (54.8%) patients. Among these, memory deficits, weakened motivation, dysosphresia and changes in temperament occurred in 18 (19.4%), 15 (16.1%), 17 (18.3%) and 40 (43.0%) patients respectively, but all these patients reported that their adverse events were tolerable and had no serious influence on their quality of life.

There was no significant difference in the percentage of occurrence of adverse events between relapse and non-relapse patients ($\chi^2 = 0.604, P = 0.437$).

Using Kaplan–Meier survival curves and the log-rank test, statistical difference was found in the 5-year survival rate between the NAc surgical group (The non-replase rate was 58%, >50%, the SPSS statistical software could not offer the value of MST and 95% CI for the NAc surgical group) and the control group (MST: 25 days, 95% CI: 16.542–33.458; Figure 3) ($\chi^2 = 142.974, P = 0.000$).

The axial and sagittal views MRI of the patient with drug dependence after surgery are shown in Figure 4. Psychological dependence may be the biggest hurdle for abstinence in drug-dependent patients¹⁰. The NAc plays a crucial and significant role in the mesocorticolimbic dopamine and addiction-related system¹¹. Gao *et al.*⁵ chose the NAc as the surgical target and obtained satisfactory results by ablating it to alleviate psychological

Table 2. Distribution of patients by category of education in non-relapse and relapse groups with NAcc surgery

Number of patients and percentile	Education			Statistical result
	Elementary school	High school	Superior or special course	
NAcc surgery (<i>n</i> = 93)	44	39	10	$\chi^2 = 4.324, P = 0.115$
Non-relapse (<i>n</i> = 58)	23 (39.7%)	29 (50.0%)	6 (10.3%)	
Relapse (<i>n</i> = 35)	21 (60.0%)	10 (28.6%)	4 (11.4%)	

Statistically significant differences between different groups. *P* (non-relapse group compared with relapse group)

Table 3. Distribution of patients by category of marital status in non-relapse and relapse groups with NAcc surgery

Number of patients and percentile	Marital status			Statistical result
	Unmarried	Married	Divorced/widowed	
NAcc surgery (<i>n</i> = 93)	26	44	23	$\chi^2 = 13.501, P = 0.001$
Non-relapse (<i>n</i> = 58)	12 (20.7%)	36 (62.1%)	10 (17.2%)	
Relapse (<i>n</i> = 35)	14 (40.0%)	8 (22.9%)	13 (37.1%)	

Statistically significant differences between different groups. *P* (non-relapse group compared with relapse group).

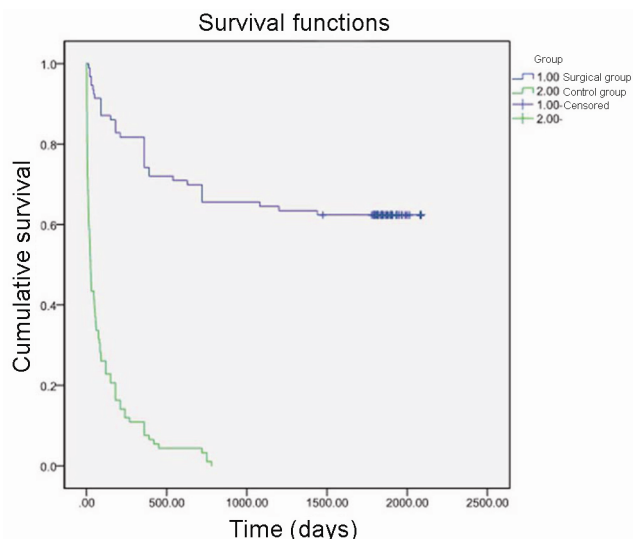


Figure 3. Kaplan–Meier survival plots of time to relapse between patients with and without surgery over a period of 5 years (*P* < 0.05).

dependence and decrease the relapse rate⁵. However, relapse was still a common and expected phenomenon in the recovery of drug dependence after NAcc surgery.

Various factors associated with relapse in drug dependence by traditional non-operative interventions have been reported in previous studies^{12,13}. It was ‘protracted syndromes’ (81.9%) and ‘insomnia’ (75.5%) were the main factors for relapse⁹. A study of relapse in heroin addicts found that social pressure (36%) was a common factor related to relapse¹⁴. In this study, the results show that there is a close correlation in factors related to relapse between the NAcc surgical group and the control group. Also, ‘relief from disturbance’ (psychological factor) and ‘peer influence’ (social factor) were the two

main factors associated with relapse among drug-dependent patients with or without NAcc ablative neurosurgery.

Our findings are similar to those of earlier studies using non-operative treatment, but our results suggest that psychological and social factors play a more important role in relapse than physical factor. First, the physical dependence could be almost alleviated after detoxification for several months, but the psychological dependence would still play a significant role in drug craving and induce the occurrence of relapse. Second, because of long-term use of drugs, drug-dependent patients always had serious problems of psychological defects¹⁵. They displayed psychological characteristics with a tendency to be emotionally fragile, sensitive and aggressive, with poor self-control¹⁶. In the present study we found that the number of patients in the employment and married status was significantly higher in non-relapse group than in relapse group at 5 years post-operation. So, relapse would be easier in patients when they are influenced by negative events in their life, such as social discrimination, employment difficulties and marriage failure.

There was a close correlation of the relapse reasons between the NAcc surgical group and the control group. There were similar relapse reasons between the two groups. We also found that the psychological factor ‘desire for last use’ was more associated with relapse in the control group than in the NAcc surgical group. Thus we may speculate that the psychological craving for drugs has been weakened in the NAcc surgical group.

We also found that ‘relief from disturbance’ (psychological factor) and ‘peer influence’ (social factor) were the two main factors associated with relapse in the two groups. We speculate that after surgery it would still be easy for the patients to relapse when they felt a negative

Table 4. Distribution of patients by category of employment in non-relapse and relapse groups with NAcc surgery

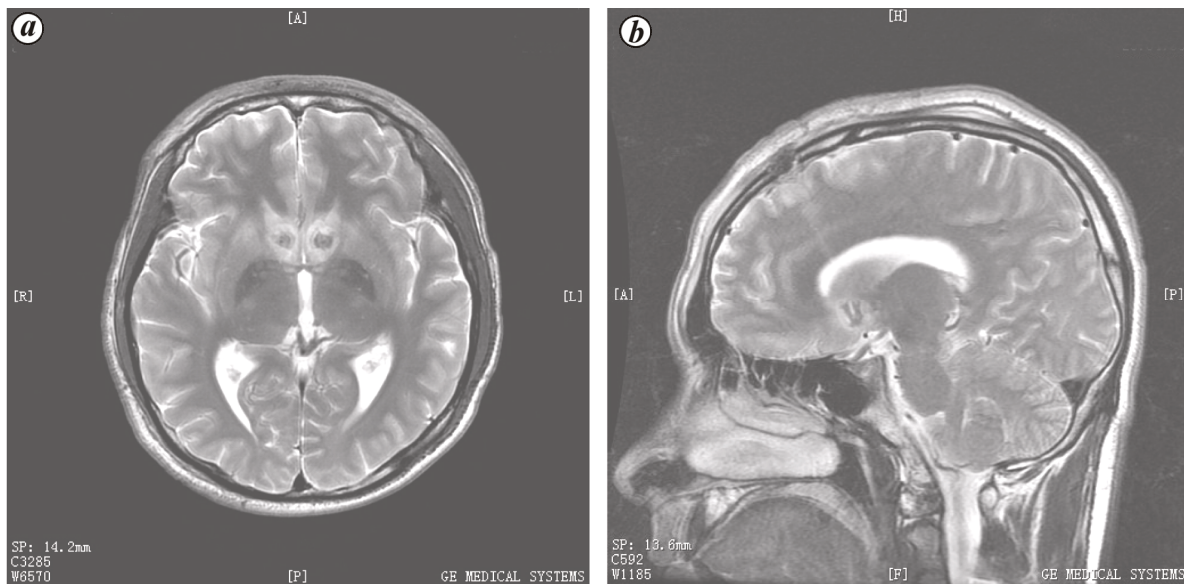
Number of patients and percentile	Employment			Statistical result
	Employed (high paid)	Employed (low paid)	Unemployed	
NAcc surgery ($n = 93$)	14	56	23	$\chi^2 = 15.115, P = 0.001$
Non-relapse ($n = 58$)	8 (13.8%)	43 (74.1%)	7 (12.1%)	
Relapse ($n = 35$)	6 (17.1%)	13 (37.1%)	16 (45.7%)	

Statistically significant differences between different groups. P (non-relapse group compared with relapse group)

Table 5. Distribution of patients by category of occurrence of adverse events (AEs) in non-relapse and relapse groups with NAcc surgery

Number of patients and percentile	With AEs	Without AEs	Statistical result
NAcc surgery ($n = 93$)	51	42	$\chi^2 = 0.604, P = 0.437$
Non-relapse ($n = 58$)	30 (51.7%)	28 (48.3%)	
Relapse ($n = 35$)	21 (60.0%)	14 (40.0%)	

Statistically significant differences between different groups. P (non-relapse group compared with relapse group).

**Figure 4.** The axial view MRI (a) and sagittal view MRI (b) of the patients after surgery.

emotion to cope with pressure. Because the brain reward system is a behavioural facilitation system, it would still activate the residual part of the NAcc if the patients reused the drugs after surgery. It would be more sensitive to drug-related cues for patients and could evoke their strong desire for drugs when they return to the past environment, see the drug tools, hear about the drugs, etc. So, the NAcc ablative neurosurgery would weaken the strong psychological desire for drugs, but it would not erase the memory about emotion with original drug addicts. The risk of relapse would be accompanied by the presence of peer influences and original milieu.

Gossop *et al.*¹⁷ reported that the average relapse time was 25 days after treatment. The relapse rate reached 71% within the first six weeks and 95% within the first three months after detoxification¹⁷. In the present study,

the median survival time in the control group was also 25 days after traditional treatment. In the surgical group, the median survival time does not exist, because the non-relapse rate is more than 50%. Although the NAcc surgery is an effective treatment to prevent relapse, a variety of adverse events occurred during the 5 years post-operation. Deep brain stimulation (DBS) would be a promising surgical therapy for the treatment of various addictions due to its therapeutic efficacy and relative lack of serious side effects¹⁷. In Tangdu Hospital, The Fourth Military Medical University, DBS has become the research focus in the treatment of addiction on the basis of the ablation neurosurgery used earlier.

It has been suggested that the best time to prevent relapse for patients would be the first three years post-operation, because we found that majority of drug-

dependent patients relapsed at that time. We speculate that in the first three years, the patients after surgery tried to return to the normal life, but faced several obstacles from the psychological and social factors. When they maintain abstinence for several years, maybe more than three years, they would get accustomed to the new life and would not relapse.

The results of the present study support most of earlier findings related to relapse in drug dependence. The study also emphasizes that two factors which have the most significant influence on relapse in drug dependence are 'relief from disturbance' (psychological factor) and 'peer influence' (social factor). The NAc ablative neurosurgery may promote effective coping strategies for treating drug dependence, and it would be helpful to reduce the relapse rate and focus on the relative time and factors associated with post-operative relapse for patients.

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Schumann resonances observed at Maitri, Antarctica: diurnal variation and its interpretation in terms of global thunderstorm activity

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Schumann resonances (SRs) are the AC components of the global electric circuit and are excited by the lightning activity within the Earth-ionosphere waveguide. An induction magnetometer, which was operated from the Indian Antarctic station, Maitri (70.8°S, 11.7°E), served to examine the SR parameters, namely the amplitude and frequency, in the north-south (H_{NS}) and east-west (H_{EW}) magnetic components. The analysis for the first resonant mode presented in this work reveals a strong UT variation in its amplitude in seasonal as well as yearly timescales. The NS amplitude reveals a semi-diurnal variation with peaks at ~1000 and ~2100 UT, whereas the EW amplitude exhibits a strong diurnal variation with a pronounced peak at 1600 UT. The diurnal curves for the frequency for

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