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RESEARCH REPORT

The influence of heroin dose and route of administration on the severity of the opiate withdrawal syndrome

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Abstract

Aims. To determine the relationship between severity of opiate withdrawal and prior heroin dose and route of administration (smoking versus intravenous injection). **Design.** Retrospective analysis of withdrawal data and assessment of associations with baseline variables including heroin dose, route of administration, duration of use, concomitant use of cocaine, severity of opiate dependence, previous treatment, sex or age. **Setting.** Psychiatric inpatient unit specialized in withdrawal treatments. **Participants.** Twenty-two opiate addicts injecting or smoking heroin who were abruptly withdrawn after admission. **Measurements.** Daily assessment of withdrawal severity with the Opiate Withdrawal Scale (OWS) during the first week after drug cessation. **Findings.** Severity and duration of withdrawal symptoms were greater in injectors compared to smokers (with comparable doses) and also in patients with higher heroin dose. Heroin dose and route of administration were related significantly to total and maximum withdrawal scores and together accounted for about 50% of variance. Similar levels of total withdrawal distress were associated with approximately five times higher heroin consumption in chasers than in injectors. **Conclusions.** The impact of heroin dose and route of administration on withdrawal severity is marked. The influence of the route of administration on withdrawal severity might be due to differences in bioavailability.

Introduction

There is considerable evidence that processes leading to physical dependence involve a readjustment of the neurobiological equilibrium to accommodate the effect of the drug. Thus, compensatory mechanisms result in a new balance of the system. When the drug is suddenly removed, unbalanced compensatory mechanisms remain and a withdrawal syndrome appears (Koob *et al.*, 1989). In the case of opiate withdrawal, it has been widely proposed that the noradrenergic system, located in the locus coeruleus, plays the

primary role. Several studies indicate that acute morphine decreases the extraneuronal levels of noradrenaline, whereas an increase in release of this neurotransmitter occurs during opiate withdrawal in several brain areas (Maldonado, 1997). From the pharmacological point of view, it seems obvious that these regulatory mechanisms depend on the degree of opioid-receptor occupation during chronic intoxication, which itself depends on plasma concentration of opiates. Thus it seems self-evident that with higher opiate doses the withdrawal severity should in-

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crease. Since route of administration is generally known to influence bioavailability of drugs, this factor should also be of substantial impact on withdrawal severity.

Not surprisingly, clinical and pharmacological textbooks mention drug dose as one major determinant of the opiate withdrawal syndrome (e.g. Goodman Gilman *et al.*, 1990; Jaffe, 1995; Martindale, 1996). However, whereas many empirical studies have been conducted on this issue, only two reports could confirm this relationship. In 1944 Andrews & Himmelsbach analysed opiate dose and withdrawal severity and found the "total abstinence syndrome for seven days" to be increased with higher morphine stabilisation dosage before cessation. The estimated relationship between the variables was not linear but, for small doses, the slope of the dose-effect curve was maximal and decreased with increasing doses. However, the authors were not able to estimate the amount of variance explained by the assumed function by statistical means. Strauss *et al.* (1976) reported that neonatal withdrawal increased with higher maternal methadone dosage, which can be taken as indirect evidence for a similar relationship in adults.

Several negative studies regarding the relationship between dosage and withdrawal severity have been published in the last two decades. Phillips, Gossop & Bradley (1986) reported that in opiate addicts who were gradually withdrawn using methadone two psychological factors, neuroticism and expected withdrawal distress, were significantly related to maximum withdrawal intensity, but dose and duration of opiate use could not be confirmed as contributing factors to withdrawal severity. Gossop, Bradley & Phillips (1987) did not find any relationship between dose and withdrawal severity. Gossop & Strang (1991) found that methadone addicts reported more severe withdrawal symptoms during both the acute withdrawal and recovery phases compared with heroin addicts, but were unable to confirm any dose effect on withdrawal intensity.

Concerning the duration of opiate use no impact on withdrawal severity has been reported (Phillips *et al.*, 1986; Kosten, Jacobsen & Kosten, 1989; Azolosa, Stitzer & Greenwald, 1995). A positive correlation between severity of naloxone-precipitated opiate withdrawal syndrome and the opiate dependence score (derived from the number of DSM-III-R criteria met), and an inverse relation to cocaine dependence

was reported by Kosten *et al.* (1989). Kosten (1990) and Rosen *et al.* (1992) concluded that acute and chronic cocaine use might reduce opiate withdrawal severity—an observation made by Freud as early as 1885.

The situation is even more complicated due to observations that heroin-taking habits have been changing in the last two decades. Smoking of heroin ("chasing the dragon") is now widespread in many European and American countries (Gossop, Griffiths & Strang, 1988; Griffiths *et al.*, 1992; Strang, Griffiths & Gossop, 1997). As far as we know, information regarding the route of administration has not been taken into consideration in recent studies. Smoking produces lower blood levels of heroin than intravenous use (Jenkins *et al.*, 1994). Thus, blood levels of heroin and opioid receptor occupation in the brain depend on dose as well as route. Therefore it is necessary to control for route of administration when examining the influence of dosage on withdrawal severity.

Despite Farrell's opinion (1994) that "opiate withdrawal is one of the longest studied and most well described withdrawal syndromes", the question of whether a relationship exists between dosage and withdrawal severity and whether smoking or injecting heroin influences withdrawal seems unresolved. The present study was designed to explore these issues by means of naturalistic data that had been recorded routinely on a detoxification ward. We hypothesized that withdrawal severity would be positively associated with higher blood levels of heroin and metabolites in the month before cessation. Therefore, withdrawal severity should be higher in addicts with higher daily heroin intake and (due to differences in bioavailability) in subjects injecting rather than smoking heroin.

Method

Study design

The study was performed in the Department of Psychiatry of the Freie Universität Berlin. Data from inpatients who were detoxified from opiates were analysed retrospectively. Opiate addicts were offered a detoxification treatment based on gradual withdrawal (with methadone or codeine) or abrupt withdrawal of opiates with the option of tricyclic antidepressants (doxepin) to alleviate withdrawal symptoms if the intensity was experienced subjectively as painful. In case of unbearable

able symptoms benzodiazepines were given additionally.

All patients meeting ICD-10 criteria for opiate dependence (WHO, 1991), who were continuously admitted between May 1994 and December 1996 were candidates for enrolment in this study. Thirty-six of these patients injected or smoked heroin as opiate of first choice. In order to achieve a more homogeneous sample, patients who were gradually withdrawn ($n = 4$) were not included. Patients who could not comply with the treatment regimen (e.g. drug relapses or continued drug consumption; $n = 2$) or monitoring scheme (missing withdrawal scores on more than 3 days; $n = 8$) were excluded from analysis.

Measurement

After admission to the hospital withdrawal symptoms were assessed daily at 8 p.m. during the first week after admission, using the Opiate Withdrawal Scale (OWS by Bradley *et al.*, 1987), a self-rating instrument for measuring opiate withdrawal distress containing 32 items with a four-point scale (nil, mild, moderate and severe).

Subjects

The included 22 patients' (17 males and five females) average age was 29.0 (SD 4.3) years (range 20–37); the duration of regular opiate use varied between 6 months and 7 years, with a mean of 3.1 (SD 1.8) years. Sixteen patients had injected heroin in the 6 months before admission and six had smoked heroin. The daily heroin dose ranged between 0.2 and 2 g with a mean dose of 8809 (SD 660) mg (street doses) during the 6 months prior to admission. Injectors consumed lower amounts of heroin than smokers (740 vs. 1250 mg). The severity of the dependence syndrome, measured by the number of ICD-10 criteria met by the patients (Langenbucher, Morgenstern & Miller, 1995), ranged between 4 (three patients) and 6 (13 patients). Ten patients had previously undergone other hospital detoxification treatments.

There was no significant difference between the 22 patients included in analysis and those 15 excluded patients regarding sex, age, route of administration, dose, severity of dependence and pre-treatment. However, patients excluded had been addicted significantly longer (duration of

regular opiate use 9.5 years, SD 6.9 years; $p < 0.001$) than those included in analysis.

All patients included in analysis received doxepin to alleviate withdrawal symptoms. The maximum dose was 300 mg/day; the mean daily dose was 158 (SD 52) mg administered over 5.3 (SD 2.2) days on average. Fourteen patients with unbearable withdrawal symptoms also received diazepam. The mean daily dose for these 14 patients was 9.5 mg (SD 6.2) over 3.0 (SD 2.4) days.

Analysis

First, analysis was performed by estimating the impact of dosage and route on withdrawal severity. In order to get the most precise estimate of association a *total withdrawal score*, based on all available scores for one subject, was computed. The total withdrawal score was calculated as mean value of all *Z*-standardized daily OWS scores, which allowed us to calculate it also for patients with missing OWS scores on some days.

Normally the effect of drugs does not increase linearly with increasing dose, but the slope of the dose-effect curve decreases with growing dose. This is also in accordance with the early report from Andrews & Himmelsbach (1944). To obtain a more linear dose-effect curve which is appropriate for the applied linear regression model we used a log transformation of heroin doses.

For statistical analysis a multiple regression analysis (backwards) with the logarithmic *daily heroin dose* (in grams) and *route of administration* (injecting/smoking) as independent variables was performed. To control the effect of other relevant clinical variables which might influence withdrawal intensity, the *severity of opiate dependence* (number of ICD-10 criteria met), *duration of regular heroin use* (in years), *regular use of cocaine* (yes/no), *pre-treatment* (inpatient detoxification yes/no), *sex* and *age* were further independent variables.

Secondly, we wanted to clarify the relationship between heroin dose and route. We assumed that the same level of withdrawal distress is associated with higher doses in heroin chasers than in injectors because smoked as opposed to injected heroin is only partially bioavailable. Therefore, we explored whether heroin smokers can consume the double, triple or even 10-fold dose as opposed to injectors, evoking the same

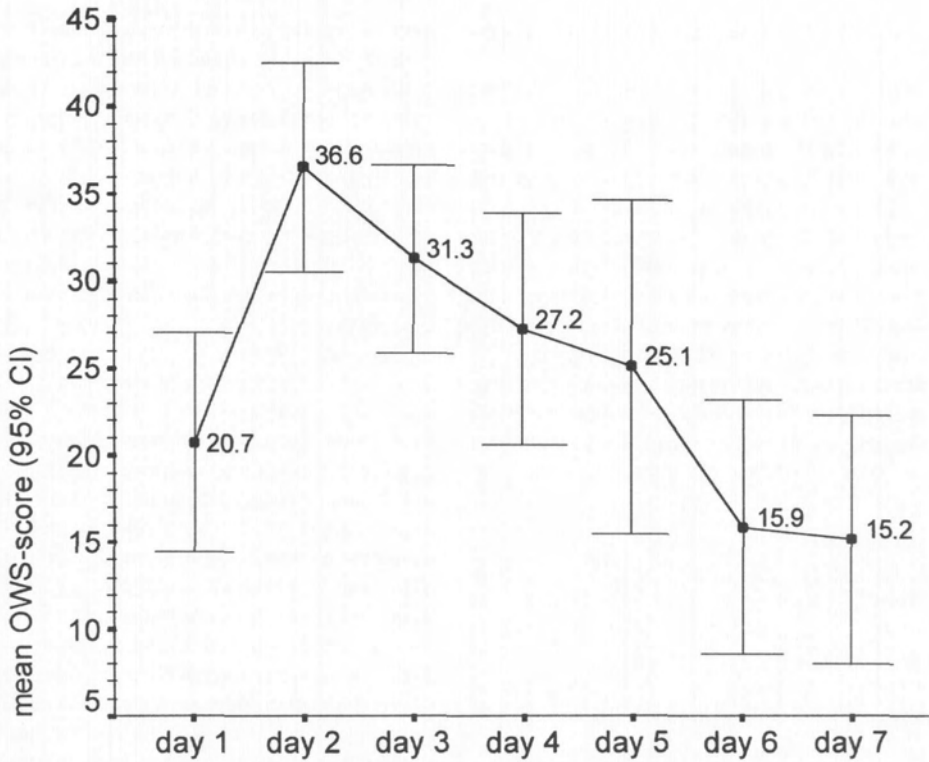


Figure 1. Course of withdrawal symptoms.

withdrawal distress. In order to receive a precise estimation of this dose-ratio we computed it from the constants (B_1 , B_2) of the regression equation. The general equation of the regression model with the two factors route and dose is: $y = C + B_1 \cdot route + B_2 \cdot \ln(dose)$ with y figuring for the withdrawal severity. Since route is coded as a dummy variable (smoking = 0; injecting = 1) withdrawal severity is given by $y_s = C + B_2 \cdot \ln(dose_s)$ for smokers and $y_i = C + B_1 + B_2 \cdot \ln(dose_i)$ for injectors. If we assume that $y_s = y_i$, the ratio of pulmonal to intravenous dosage is given by $dose_s/dose_i = e^{**}B_1/B_2$. Thus in smokers compared to injectors the ($e^{**}B_1/B_2$)-fold heroin dose is associated with the same level of withdrawal distress; looking it from a different angle only the ($e^{**}B_1/B_2$)-th part of smoked heroin is "effective" regarding withdrawal severity.

Thirdly, the impact of the previously identified model of dosage and route on the course of withdrawal symptoms was analysed. Therefore the *effective dose* of heroin was calculated by dividing the dose for subjects using the pulmonal

route by the previously obtained dosage ratio and the dose for subjects using the intravenous route by 1. Then the bivariate correlation between the logarithmic effective dose and each of the seven daily OWS scores and the maximum withdrawal score obtained for each subject was computed.

The results reported here refer to a level of significance of 0.05. Since our hypotheses regarding dosage and route were all directed, p -values given refer to one-tailed tests.

Results

The clinical description of the course and severity of the opiate withdrawal syndrome is given in Fig. 1. After abrupt withdrawal from opiates symptom severity rose from a moderate level on day 1 of hospital treatment to the peak value on day 2 (OWS mean score was 36.6; SD 13.5). During the next 5 days the mean score declined steadily to a value of 15.2 (SD 13.9) on day 7. It should be mentioned here that the individual

peaks of withdrawal severity were reached between day 1 and day 5.

Multiple regression analysis revealed that both variables—logarithmic *heroin dose* ($\beta = 0.63$; $p < 0.001$) and *route of administration* ($\beta = 0.66$; $p < 0.001$)—were significantly related to the total OWS score. Interestingly, the beta weights of both variables were higher than the corresponding zero-order correlations with the total OWS score ($r = 0.41$ resp. $r = 0.45$). This indicates a reciprocal suppression of dose and route. As expected, the withdrawal intensity was increased with higher doses and with intravenous application of heroin; withdrawal intensity was decreased with low doses and in heroin chasers. Both variables together accounted for 55% of the total score variance ($F = 11.8$; $df = 2/21$; $p < 0.001$). None of the other variables (severity of opiate dependence, duration of regular heroin use, regular use of cocaine, pre-treatment, sex and age) was significantly linked with total withdrawal severity. The estimated ratio of smoked to injected heroin dose was 5.15, indicating that the same level of total withdrawal distress was associated with approximately five times higher doses in chasers than injectors. This relationship can also be seen from the scatterplot in Fig. 2. Since the regression lines for intravenous and pulmonary use are nearly parallel and the dosage scale is logarithmic, this implicates that the dose relation between both subgroups are nearly similar over the whole range of withdrawal severity.

The logarithmic *effective heroin dose* accounted for 52% of variance of the maximum withdrawal score for each subject, which was highly significant ($r = 0.72$; $p < 0.001$). It can be seen in Fig. 2 that the maximum withdrawal scores were about 21 points higher in injectors than in chasers who had reported the same consumption of heroin.

The analysis of the time course of withdrawal revealed that the impact of logarithmic effective heroin dose was high for all days except the first one (cf. Table 1). Correlation coefficients were found to be significant from day 2 ($r = 0.50$) up to day 7 ($r = 0.62$). The strongest effect could be shown for day 6, when 51% ($r = 0.71$) of the variance of the OWS scores was explained by the effective heroin dose.

Discussion

Our data indicate clearly that the opiate withdrawal syndrome (indicated by the total and

maximum withdrawal scores in this study) was influenced by the daily heroin doses the patients reported to have consumed (during the month prior to hospital detoxification). Following several other studies, which had failed to report a relationship between dose and withdrawal severity, this is the first replication of an early report by Andrews & Himmelsbach in 1944.

To the best of our knowledge, this is the first empirical study also demonstrating that intravenous administration was linked with greater total and maximum withdrawal severity than smoking the same amount of heroin. Maximum withdrawal scores were about 21 points higher (equivalent to seven severely presented symptoms) in injectors than in smokers for the same reported amount of heroin. The statistical model we applied allowed us to assume that a similar level of withdrawal distress is associated with an approximately five times higher dose in addicts if they smoke heroin compared to the condition of injecting the same drug. Therefore, only a fifth of the dose consumed by chasers seems to be effective, which may be due to a bioavailability of approximately 20%. Other estimates in literature had ranged between 12% and 100% bioavailability (Mo & Way, 1966; Jenkins *et al.*, 1994), but technical difficulties obscured more precise estimations. Besides differences in bioavailability, pharmacokinetics and pharmacodynamics of smoked heroin are reported to be quite similar to injected heroin (Jenkins *et al.*, 1994). Thus the effect of route may solely be due to lower bioavailability of smoked as compared to injected heroin.

Analysing withdrawal over time, a substantial impact of both variables "dose" and "route of administration" on withdrawal scores could be demonstrated for all days after drug cessation, except the first day. This might be due to the fact that some addicts already experience withdrawal symptoms on admission, whereas others have just taken their last dose shortly before, so that withdrawal symptoms start some hours later. The relevance of both factors during days 5–7, when withdrawal intensity was already declining, was due to the observation that several patients (who had smoked low doses of heroin) already reached baseline levels of withdrawal whereas others (who had injected high doses of heroin) were still experiencing severe withdrawal symptoms. Therefore, not only intensity but also dur-

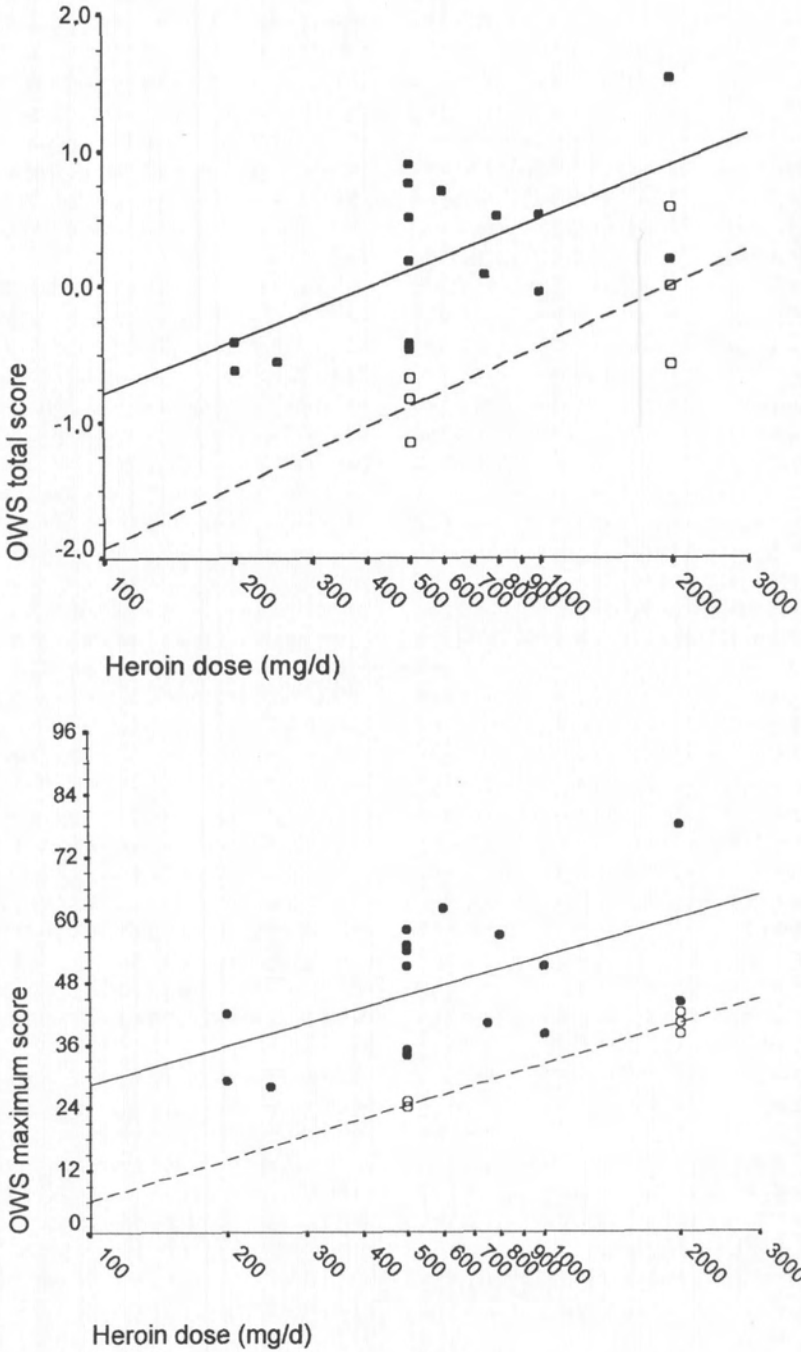


Figure 2. Scatterplot of heroin dose and withdrawal severity. ■, Injectors; □, Smokers.

ation of withdrawal symptoms seems to increase with higher doses and intravenous use.

Taking into consideration why former research groups were unable to demonstrate dose-related

effects during opiate withdrawal (Phillips *et al.*, 1986; Gossop *et al.*, 1987; Gossop & Strang, 1991), several circumstances have to be discussed. First, heroin addicts and polydrug users

Table 1. Correlation of effective heroin dose with withdrawal severity on different time points

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Max.
0.05	0.50**	0.57**	0.59**	0.68***	0.71***	0.62**	0.72***

Day 1 is the day of opioid cessation, day 2 is the following day, etc.; max indicates the maximum withdrawal score observed in each subject. **Correlation is significant at the 0.01 level (one-tailed); ***correlation is significant at the 0.001 level (one-tailed).

are obviously those patients who are most difficult to study due to drop-outs and the inability of many individuals to co-operate with diagnostic, therapeutic or experimental requirements in psychiatric wards obscuring the relationship of dose and withdrawal severity. Secondly, tapering dosages of methadone were given in former studies, whereas we withdrew heroin abruptly and assisted withdrawal with antidepressants. The only study which previously reported a positive dose withdrawal relationship (Andrews & Himmelsbach, 1944) also analysed patients who were abruptly withdrawn. The methadone tapering in the recent studies might have obscured dose-withdrawal relationships because subjects with higher stabilisation doses were also receiving more methadone during withdrawal. Thus the higher the stabilization dosage, the higher the withdrawal suppressing effect of the methadone tapering was. This might explain why Phillips *et al.* (1986) as well as Gossop *et al.* (1987) even observed a trend towards a negative relationship between dose and withdrawal severity. Thirdly, the statistical approach was different in our study. In studies who found no linkage, a linear dose withdrawal relation was assumed. We, on the other hand, decided to use a logarithmic model, which is in accordance with the findings of Andrews & Himmelsbach (1944). Our data indicate that this is more suitable because correlations with log transformed doses are higher than with non-transformed doses. We also included the route of administration in a multivariate statistical analysis. Since dose and route are reciprocal suppressor variables, the non-inclusion of route would have masked the effect of dose in our sample. Similarly, we would not have found any impact of dosage on total and maximum withdrawal if we had only calculated the bivariate correlation between dose and withdrawal severity.

However, a certain shortcoming of this study is

its naturalistic and non-experimental design. It could be argued that the analysis of dose-withdrawal relationship in this study might be flawed by the individual medication the patients received only for reducing withdrawal symptoms. Since doxepin is equipotent to clonidine in alleviating opiate withdrawal (Täschner, 1986), it can be assumed that our medication suppressed withdrawal symptoms and led to reduced withdrawal scores. Analysing the relation between medication and withdrawal severity showed that the cumulated doses of antidepressants and diazepam were highly positively correlated with the total withdrawal score ($r = 0.73$; $p < 0.001$; resp. $r = 0.51$; $p < 0.05$). Supposing that the withdrawal suppressing effect of the medication increases with higher doses it can be concluded that the differences among subjects would have been even more pronounced if no drug treatment had been applied. We therefore assume that our results are not artefacts due to medication.

Another limitation of the study is the length of the period studied, with it being restricted to the observation of only 7 days when the patients' discomfort has usually not been relieved completely. In further studies, it would be most desirable to analyse longer withdrawal periods of heroin addicts, allowing the collection of more information on complaints and underlying mechanisms needed to improve therapy during the different phases of opiate withdrawal.

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