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ORIGINAL INVESTIGATION

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Time series modeling of heroin and morphine drug action

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Abstract *Rationale:* Clinical observations and recent findings suggested different acceptance of morphine and heroin by intravenous drug users in opiate maintenance programs. We postulated that this is caused by differences in the perceived effects of these drugs, especially how desired and adverse effects of both drugs interacted. *Objectives:* We measured the desired and adverse effects of high doses of injected morphine and heroin in patients to determine the causal interactions between both types of effects and test the hypothesis of a differential mechanism of action. *Methods:* Thirty-three patients (five females, 28 males; mean duration of previous street heroin use 10.7 years, mean age 30.1 years) were randomly allocated double-blind to the substance groups. The average daily dose per participant in the heroin condition (n=17) was 491 mg, in the morphine condition (n=16) 597 mg. The observation period lasted 3 weeks; an average of 70 injections was received. After each injection of either substance, various aspects of drug effects were recorded systematically. Ratings were summarized into the factors "euphoria" and "adverse effects". Time series models were computed for each participant on the basis of the factor scores, using vector autoregression (VAR). *Results:* A highly significant difference between the substances was found in the interaction between "euphoria" and "adverse effects". Adverse effects of heroin preceded higher euphoria, whereas adverse effects of morphine preceded subsequent lower euphoria. Additionally, the finding of a higher level of adverse effects in morphine was replicated. *Conclusions:* Results point to different mechanisms of action of the two opioids when the perceived drug effects are evaluated in a field setting. This may explain the better acceptance of heroin in opiate-assisted treatment of intravenous drug patients. The method used can be a valuable tool for the comparison of substance groups other than opioids.

Keywords Heroin · Morphine · Maintenance drug treatment · Perceived mechanism of action · Time series analysis

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Introduction

The use of opiates as psychotropic agents is a societal concern in many countries. Because of the severe medical, social, and psychological hazards entailed by opiate use, a large number of treatment approaches have been developed that are well covered by psychiatric and psychological publications. Relatively little, however, is known of the behavioral and experiential effects of these drugs, especially when opiates such as heroin or morphine are taken habitually and in high dosages. Our review of the literature (based on PsycINFO and MEDLINE searches of heroin-related journal papers) showed that among several hundreds of articles on human users, virtually none addressed the perceived mechanisms of action of these drugs. Studies of drug-induced mood changes, such as that of Lasagna et al. (1955) and of the research group at the Alcohol and Drug Abuse Center at McLean Hospital in Belmont, Mass., USA (McNamee et al. 1976; Mirin et al. 1976), are rare exceptions. Interestingly, both groups reported that dysphoria has to be considered as a rather common effect of heroin, which stands in contrast to the general belief that heroin is a highly euphoriagenic substance.

This absence of published research is, of course, due to ethical and legal considerations that rule out consumption of heroin even under experimental conditions. Additionally, non-confounded data on the effects of consumption by illicit users are almost inaccessible for scientific description. Therefore, the project reported here took the opportunity to investigate (self-) observed drug effects

and their mutual interactions in the framework of a research project that was centered on investigating maintenance therapy with opiates.

In 1994, following a long period of political debate, the Swiss Federal Office of Public Health implemented this nationwide research project, the Program for a Medical Prescription of Narcotics (PROVE), to study the intravenous application of heroin, morphine, and methadone in chronic drug users. The scientific goal of PROVE was to determine how patients respond to the maintenance prescription of injectable opiates, and to investigate the pharmacology of these substances as well as the feasibility of controlled dispensing. Meanwhile the Swiss drug maintenance program has passed its initial implementation stages; currently, more than 1000 drug users are included in programs that provide injectable opiates in Switzerland (Uchtenhagen et al. 1999; Rehm et al. 2001, Rihs-Middel et al. 2002).

Within the context of PROVE, a double-blind study was performed to evaluate the effects and side effects of high-dose heroin and morphine in a sample of intravenous drug users. Of two double-blind study groups, group A was started on a small dose of a 3% morphine solution. The dose was gradually increased up to an individual maintenance dose and adjusted to meet the participants' subjective needs for opiates. On a randomly determined day in the third or fourth week of the study the participants were switched double-blind to the same volume of a 2% heroin solution. This concentration is considered as equipotent (Haemmig 1997, discussed in Haemmig and Tschacher 2001). Group B started with heroin and was later switched to morphine using the same protocol. The study lasted a total of 6 weeks for each participant. All drug injections took place on the premises of the outpatient drug clinic KODA-1 in Bern, Switzerland. The cross-sectional results of this study have been published by Haemmig and Tschacher (2001). They found that, compared to morphine, heroin produced significantly lower degrees of itching, flushing, urticaria and other adverse side effects. The heroin condition resulted in higher desired, euphoric drug effects, but this difference failed to reach statistical significance. The rate of premature discontinuations by study participants was markedly larger in the morphine condition.

Apart from cross-sectional data, the double-blind study provided rich documentation on each of the numerous single drug injections. In other words, there is ample additional information about the participants' immediate reactions to the repeated administrations of either of the two drugs. It is postulated here that this time series information can reveal the phenomenal mechanisms of drug action during maintenance therapy. These data express how the underlying physiological properties of the opioids have been translated into phenomena that could be perceived by the users themselves and by staff. We were especially interested in the manner by which desired effects and adverse effects, of both heroin and morphine, interacted; possible differential interactions of the two aspects of drug action might explain the difference of approval of high-dose heroin and morphine that was found in the cross-sectional investigation. In the present paper, we therefore computed time series models to describe the process of observed drug action and to distinguish the expected differential consequences of heroin and morphine.

Materials and methods

Sample

Thirty-nine applicants were selected for inclusion in the double-blind study, 31 males (79.5%) and eight females (20.5%). Inclusion criteria for participation were long history of intravenous opioid abuse (at least 2 years of continuous injecting of illicit heroin prior to entry into the program), at least two failed treatment attempts (detoxification, rehabilitation or methadone maintenance), a minimum age of 20 years, and local residency. Applicants gave their written informed consent prior to inclusion in the study. The study design was approved by the Ethics Committee of the Medical Faculty of the University of Bern and by the Swiss National Ethics Committee.

For the time series investigation reported here, 33 of these 39 participants were considered (84.8% male, 15.2% female), of whom 17 were randomized into the heroin condition and 16 into the morphine condition. For methodological reasons, the inclusion criteria of the present study were as follows. First, the lengths of observation were 35 or more points of measurement in order to allow time series modeling; participants with fewer points of measurement (owing to premature discontinuation) were excluded. Second, only the data prior to crossover were evaluated in order to avoid selective data sets. Because of many discontinuations after crossover, especially in participants switched from heroin to morphine, the sample remaining after crossover was highly selective. This would have caused a considerable bias. In addition to this, blinding was less successful after crossover.

The average daily dose per participant in the heroin condition was 491 mg (SD: 199 mg) and in the morphine condition 597 mg (SD: 338 mg). Patients in the morphine condition (n=16) and the heroin condition (n=17) did not differ with respect to age at entry into the study (mean age of morphine group 30.1 years, SE 5.1 years, mean age of heroin group 30.1 years, SE 5.3 years; t=–0.049, P=0.96), duration of street heroin use (mean duration of morphine group 10.6 years, SE 4.9 years, mean duration of heroin group 10.8 years, SE 5.5 years, t=0.099, P=0.92), and gender distribution (Mann-Whitney U-test, P=0.58). Thus, the randomisation was successful.

Data acquisition

After each injection of either heroin or morphine, various aspects of drug effects were recorded systematically using 23 different measures. Both objective and subjective data on the drug effects were considered in this investigation. The measures were based on observations of the staff of the drug clinic (12 items) as well as on reports of the participants themselves (11 items).

The nurse or physician administering the injection rated side effects such as flushing, hives, edema, itching, "pins and needles" sensation, and other adverse reactions according to their location/spread and intensity. Both location/spread and intensity were coded on three-point scales.

Additional data on drug effects and side effects were derived from participants' self-reports of their perceptions of drug action. An adapted Osgood semantic scale with seven-point Likert scales was used. The following items were recorded: perceptibility of drug effects; "rush"; euphoria or relief; feeling clear-headed or functioning better than before; feeling well-balanced or relaxed; inner

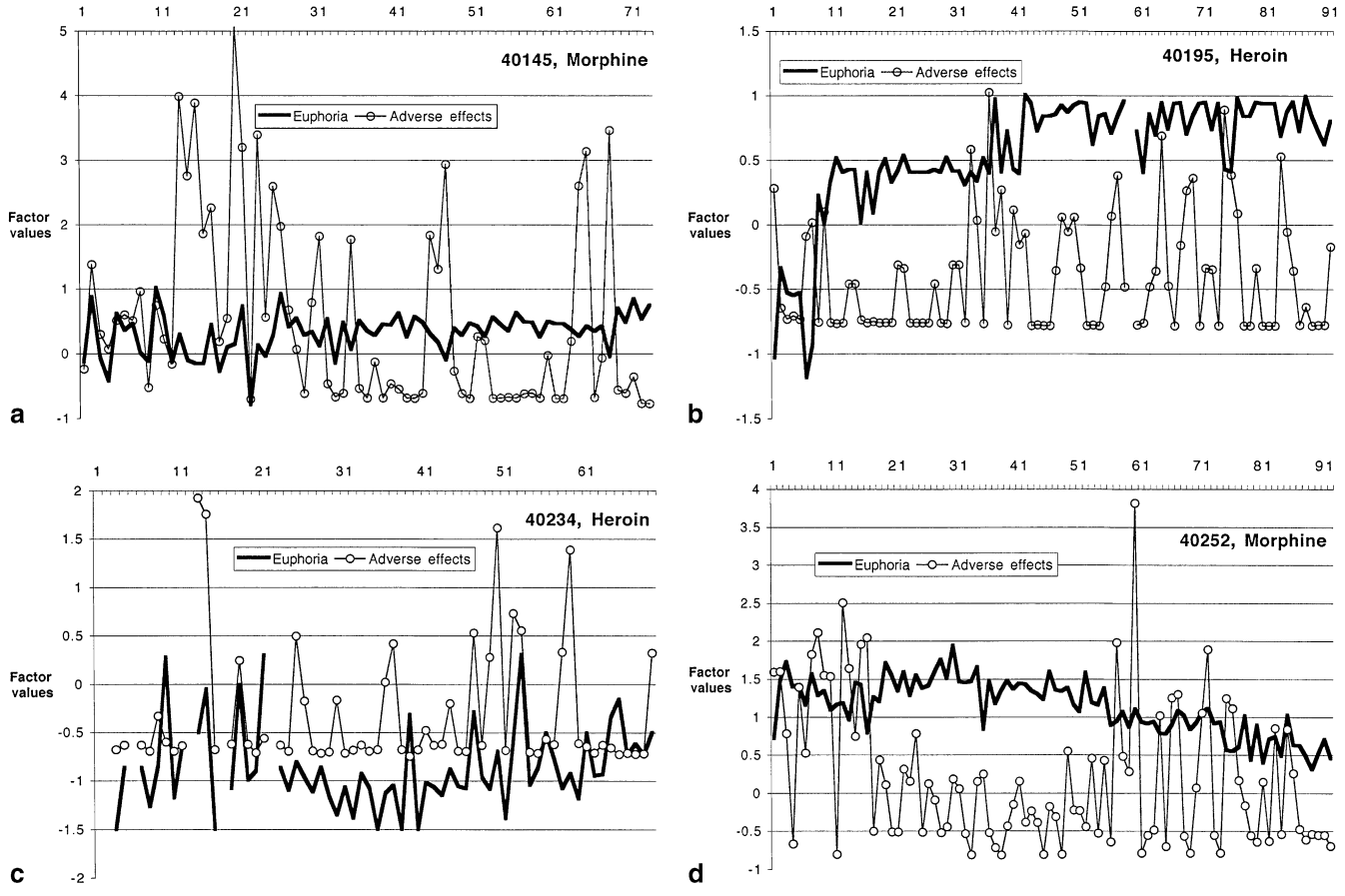

Fig. 1a–d Examples of time series of four participants

warmth; itching or prickly sensation ("pins and needles"); frustration; nausea; vertigo and headache.

The data sets of the participants comprised between 36 and 125 points of measurement (mean 70, SD=19) that were distributed over the 3-week observation period of the study prior to cross-over. Thus, on average, there were between 3 and 4 points of measurement per day and participant.

Principal component analysis (PCA)

The 23 items of drug effect measures were factor-analyzed by PCA in order to summarize and reduce the number of variables. To keep the complexity of the models manageable, we extracted only two factors knowing that they would contain the desired and the adverse effects, respectively. The items frustration, nausea, vertigo and headache were not used in the present investigation because of their low variances that caused low communalities in the PCA. The two factors accounted for approximately 48.7% of the sample's total variance. The factors were obtained using orthogonal ("varimax") rotation. We labeled the rotated factors "euphoria" (25% explained variance) and "adverse effects" (23.7% explained variance).

The values of "euphoria" rest on the participants' evaluations of perceived desired drug effects. "Adverse effects" consist of participants' reports of itching and stinging sensations as well as the nurses' observations of the histamine-induced skin effects (the intensity and spread of reddening, hives, and edema). Thus, in accordance with the goals of the present investigation the two PCA factors enabled us to quantify the degrees of desired and of adverse reactions to heroin and morphine at any point of measurement.

Time series analysis

Based on the PCA results, we computed the factor scores for each participant as the linear combination of all items loading on a factor. Factor scores were obtained at each point of measurement, i.e. at all the times when an injection was given. Examples of the resulting bivariate time series are shown in Fig. 1.

Time series analyses of the factors euphoria and adverse effects were performed for each of the 33 participants. The time steps were natural units given by the series of subsequent injections each participant received. We computed vector autoregressive models of second order (so-called lag 2 VAR models) throughout the sample by using the VARMAX procedure of SAS© software. The standardized modeling of all time series assured comparability across all participants, which is a necessary condition for later aggregation of the models across the sample (panel analysis, cf. Tschacher and Jacobshagen 2002).

This method is called vector autoregression (VAR) because each time step of the observed process (in our case, each point of measurement describing an injection of a drug) is given by a vector composed of several scalar components (in the present study, two factors). A VAR model determines the regressive association of each vector (containing the two factors euphoria and adverse effects) at time t–2 and t–1 with the vector at the subsequent time of measurement t. Vector autoregression therefore includes regressions of one factor to the other (for instance, the interaction of euphoria[t–2] with adverse effects[t]) as well as the autocorrelations that denote the impact of each factor on itself at the subsequent points of time. Together with these four autocorrelations, the time series analyses yielded eight VAR parameters per participant, which quantified the strength of the sequential associations. In addition to that, the VARMAX procedure estimates linear

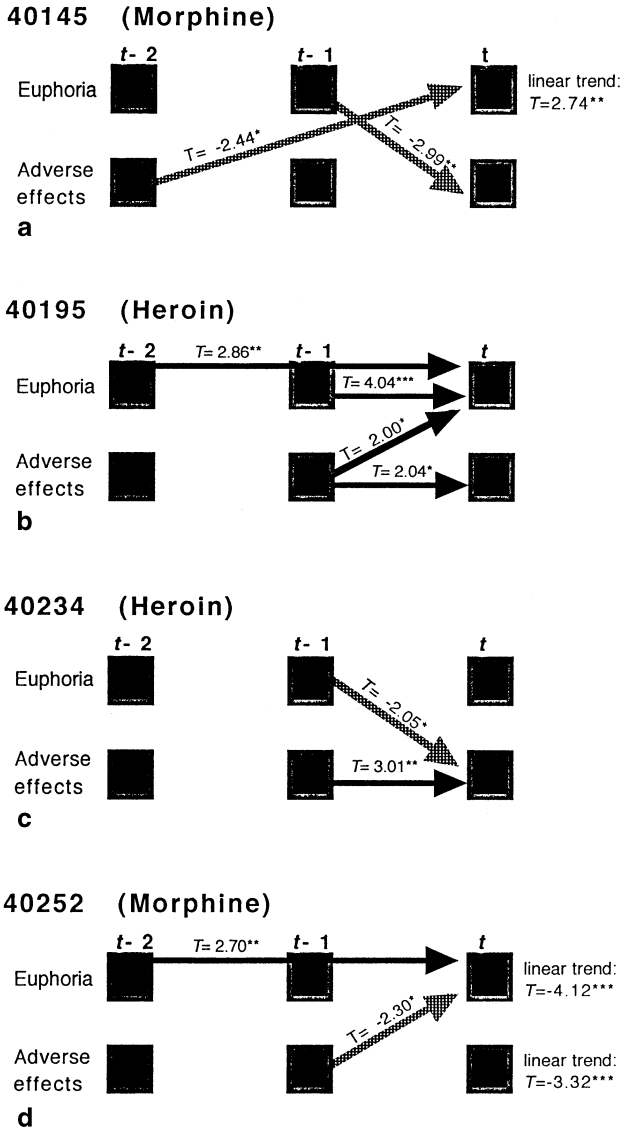

Fig. 2a–d Individual models for each of the time series displayed in Fig. 1. *Arrows* indicate significant interactions between factors. The respective *t*-values are given by numbers (*$P<0.05$; **$P<0.01$). Negative interactions have *dotted arrows*. Time-lagged interactions are symbolized by arrows starting from a factor score at time *t*–1 or time *t*–2 to the factor score at time *t*. Each *t* is the time of an injection (the points of measurement)

trends (slopes) for both factors. Each of the resulting ten parameters is given by its *T*-value (defined as the parameter weight divided by its standard error). The time series dynamics of each participant was thus completely described by a set of ten parameters (four interactions, four autocorrelations, two trends). In random processes, these *T*-values are distributed normally around an expected mean value of zero, which would indicate no sequential interactions, no autocorrelations, and no trends.

Thus, the time series model of each participant (with either heroin or morphine) can be expressed by these parameters. We evaluated a "prototypical" time series model by evaluating the parameters of all participants in the heroin and in the morphine conditions. In other words, we investigated if the subsample mean of a parameter's *T*-value deviated significantly from zero. Such significant deviations reflect the average dynamics of either substance in this sample. Additionally, the parameters of the

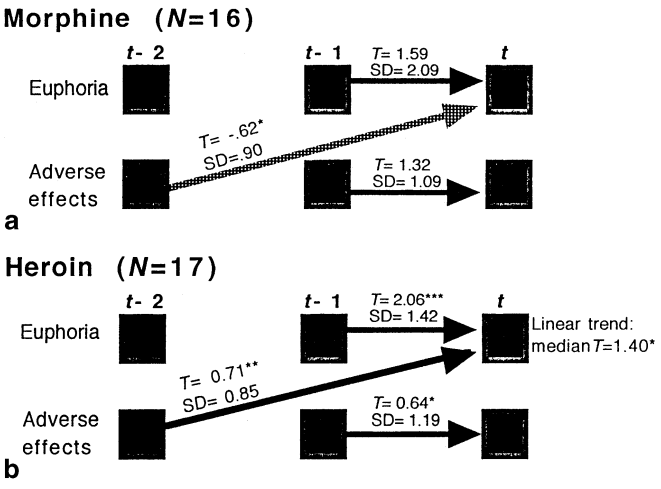

Fig. 3a, b Average time series models for the heroin and morphine condition (cf. legend of Fig. 2)

substance conditions were compared using multivariate analysis of variance and univariate *t*-tests for independent samples (Wilcoxon tests were used where appropriate).

Results

Figure 2 presents the individual time series models of those participants whose process data are displayed in Fig. 1. Some heterogeneity is expressed in these results. For example, the dynamics of participant 40252 who was placed in the morphine double-blind condition is characterized by adverse effects entailing lower euphoria at the next point of measurement (diagonal dotted arrow in Fig. 2d). In participant 40195, who received heroin, adverse effects preceded higher euphoria (diagonal arrow in Fig. 2b).

In order to deal with the individual variation of time series models, we first computed average time series models for each of both drug conditions. The results are presented schematically in Fig. 3a, b; all means and standard deviations are given in Table 1. Second, multivariate analysis of variance (MANOVA) with subsequent univariate *t*-tests allowed the assessment of the presence of systematic differences between the actions of the two drugs (Table 1).

Figure 3 shows that in both drug conditions positive autocorrelations of euphoria and adverse effects were found which pointed to sequential stability of the factors: if euphoria or adverse effects were expressed to a certain degree at one time, it was likely that they would be experienced similarly at the subsequent point of measurement. These autocorrelations of the two factors were independent of one another. In the heroin condition, a positive trend was found for euphoria, thus there was a general increase of euphoria with time. Adverse effects were expressed significantly higher in morphine compared to heroin.

Table 1 Means (M) and standard deviations (SD) of time series parameters. The sequential association of each of the two factors euphoria and adverse effects at time *t*–1 and time *t*–2 with these factors at the subsequent time of measurement *t* (in short notation, e.g. adverse effects [*t*–1]→euphoria[*t*]) is quantified by the *t*-values provided by time series analyses in each patient

VAR parameter	Heroin group *M* (*SD*)	Morphine group *M* (*SD*)	*t*-Tests heroin vs morphine[a]
Euphoria [*t*–1]→euphoria [*t*]	2.06*** (1.42)	1.59** (2.1)	*t*=0.75 (*P*=0.461)
Euphoria [*t*–2] →euphoria [*t*]	0.49 (1.32)	0.84 (1.77)	*t*=0.65 (*P*=0.518)
Adverse effects [*t*–1] →adverse effects [*t*]	0.64* (1.19)	1.32** (1.1)	*t*=1.70 (*P*=0.099)
Adverse effects [*t*–2] →adverse effects [*t*]	–0.17 (1.06)	0.02 (0.91)	*t*=0.57 (*P*=0.575)
Euphoria [*t*–1] →adverse effects [*t*]	–0.01 (1.06)	–0.41 (1.42)	*t*=0.93 (*P*=0.359)
Euphoria [*t*–2] →adverse effects [*t*]	0.01 (1.27)	0.01 (1.35)	*t*=0.00 (*P*=0.999)
Adverse effects [*t*–1] →euphoria [*t*]	–0.09 (1.44)	–0.16 (1.26)	*t*=0.14 (*P*=0.892)
Adverse effects [*t*–2] →euphoria [*t*]	0.71** (0.85)	–0.62* (0.9)	*t*=4.39 (*P*<0.001)
Linear trend of euphoria	1.00*[b] (1.96)	0.39 (2.33)	*t*=0.81 (*P*=0.422)
Linear trend of adverse effects	–0.81[b] (1.45)	–1.15* (2.13)	*t*=0.54 (*P*=0.593)
Constant of euphoria	–0.99 (3.05)	–0.19 (3.51)	*t*=0.70 (*P*=0.491)
Constant of adverse effects	–0.82 (2.18)	1.09 (2.10)	*t*=2.53 (*P*=0.016)

Asterisks, test of the null hypotheses that mean VAR parameters were zero (*P<0.05; **P<0.01; ***P<0.001). *t*-Tests, univariate comparisons of substance groups

[a] Whole model test of difference was significant [MANOVA $F(10,22)=2.38$, $P=0.044$)]

[b] Wilcoxon test was used because of non-normal distribution

In addition to autocorrelations and trends, however, the factors were associated by a lag 2 interaction, namely the interaction between adverse effects at *t*–2 and euphoria at *t*. This interaction was positive in the heroin condition and negative in the morphine condition. In other words, adverse effects of heroin preceded higher euphoria, whereas adverse effects of morphine preceded subsequent lower euphoria.

The result of the MANOVA whole model test was significant [$F(10,22)=2.38$, $P=0.044$]. Thus, the time series models differed with respect to the substance subgroups. The univariate additional tests highlighted the highly significant difference between the drugs in the parameter adverse effects [*t*–2]→euphoria [*t*] which survived conservative application of Bonferroni alpha adjustment.

Discussion

The evaluation presented here was based on a double-blind randomized study of drug effects. Two independent groups were defined, 17 participants receiving heroin, and 16 participants receiving morphine. The objective of this evaluation was to assess the interaction between positive drug effects (euphoria) and negative drug effects (adverse effects) in each group, and then compare these groups. It is important to note that these assessments were not simply derived from the mean levels of the various drug effects, but from the dynamics of the complete process of administering the drugs. The advantage of this approach is its increased ecological validity. Events in everyday life as well as in any kind of treatment occur in specific temporal sequences and patterns; detection of such patterns is (or should be) essential in scientific inquiry. Therefore, this study is based on time series parameters that could be computed for each single participant by application of vector autoregression.

The rationale for this kind of study was to uncover the dynamics of drug responses on the grounds of how these responses were experienced and observed by the participants and by staff. We expected that a possible causal mechanism inherent in the responses to both drugs during maintenance therapy could be found on this "phenomenological" level. The evidence corroborated this expectation; the temporal interactions of euphoria and adverse effects were strikingly different in heroin and morphine.

Before we discuss this finding, we should point to a premise underlying possible interpretations. One may be tempted to equate temporal sequences with causal sequences. This premise must be considered with caution because the argument "post hoc ergo propter hoc" (i.e. the argument "if B happens after A, A caused B") is invalid. Nevertheless, temporal sequences may provide empirically based hypotheses on causal interactions, especially if specific sequences are found significantly more often than competing sequences in a time series analysis, and if alternative explanations are unlikely. In psychosocial and medical settings, strict experimental control of all constraints and variables that could exert causal influences is often not feasible. Therefore, process analyses, in addition to their ecological validity, have great potential as methods that can produce hypotheses about causal relationships even when only field observations are available.

A further point worth considering is whether the participants were in fact blind to the substances they received. As a part of the protocol, the participants were routinely and explicitly asked to guess which substance had been injected. On average, such guesses were correct on 56% of all occasions (incorrect, 17%; "do not know" or missing, 27%). In the absence of any feedback from staff, the percentage of correct guesses increased during the protocol and after crossover. In our view, even though the probability of correct identification was above chance level, the study (especially prior to cross-over) was not generally unblinded. In addition to this, it is unclear in

which way this could have biased the interaction between drug effects focused on in this study. We conclude that recognition of the drug is unlikely to provide an alternative explanation of the present findings.

With the aforementioned interpretational caveats in mind, we may discuss our finding that the dynamic interaction between euphoria and adverse effects of the opioids depended on the drug administered. Under heroin as well as morphine, adverse effects were coupled with euphoria when two time lags were considered in the analysis. These interactions, however, had opposite values. Under morphine the presence of adverse effects preceded a lowered degree of euphoria, thus, in causal parlance, adverse effects lowered euphoria. In the heroin condition, adverse effects preceded a higher degree of euphoria; adverse effects enhanced euphoria. We may conclude that tolerating morphine-induced adverse effects was discouraged by a subsequent weakening of the desired effects of morphine, and that, conversely, tolerating heroin-induced adverse effects was reinforced by a subsequent increase of euphoria. When using heroin, even the unwanted effects may obtain signal quality to the user that the desired euphoric effect will arrive soon. Together with our present and previous (Haemmig and Tschacher 2001) findings showing the overall level of adverse effects to be higher in the morphine condition, this may explain the better acceptance of heroin in opiate-assisted treatment of intravenous drug users. This is important, because the acceptance of a treatment regimen by the patients enhances their compliance. The method employed in this study allowed the detection of differences between two substances with basically very similar modes of effect that were not evident in pharmacokinetic models and clinical considerations. Thus, we foresee that time series methods would also prove to be valuable tools to assess differences in effects of other groups of medications such as neuroleptics or antidepressants.

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