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Effects of chronic treatment with methadone and naltrexone on sleep in addicts

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Abstract Previous studies have described sleep disturbance secondary to chronic opiate use and abuse. Drug-dependency insomnia is of interest because chronic sleep disturbances can promote depressive symptoms which could lead to a drug relapse. For the first time we compared the polysomnographic parameters of 10 methadone-substituted outpatients and 10 naltrexone-treated outpatients. Methadone (μ-opioid agonist) produced a marked fragmentation of the sleep architecture with frequent awakenings and a decrease in EEG arousals. In comparison with methadone and controls, the naltrexone (μ-opioid antagonist) group showed the shortest sleep latency and the longest total sleep time. These data indicate that μ-agonists and μ-antagonists have different effects on sleep. The implications, especially the involvement of opioid-dopamine interactions on sleep and movements during sleep, are discussed.

Key words Sleep disturbance · Methadone · Naltrexone · Opioid-dopamine interaction

Introduction

Due to the increasing number of fatalities among drug addicts in Germany (Poser et al. 1992; Püschel 1993), we started in 1990 our methadone project. The treatment strategy with methadone (μ-agonist) substitution should give heroin addicts a realistic chance for survival and therefore the possibility to change the psychosocial surroundings. In a second step the motivation for abstinence should be achieved by psychosocial stabilisation. To prevent the re-abuse of heroin after detoxification the μ-receptor-antagonist naltrexone was offered. To date, 182 methadone outpatients and 239 naltrexone outpatients underwent our treatment. Figure 1 shows the retention in the treatment program. Almost 50% of the methadone outpatients remained up to 600 days in the program. In comparison 50% of the drop out occurred in naltrexone outpatients within the first 50 days (see Fig. 1). This drop out rate is comparable to other studies: Shufman et al. (1994) reviewed the literature and found a median length of retention of approximately 60 days.

Besides the pure pharmacological event of heroin addiction, the retention rate is influenced by psychosocial factors. For example, Capone et al. (1986) found a better outcome in patients with a stable job situation during the treatment program. Thus, there is general agreement that it is difficult to assess the efficacy of opiate maintenance and abstinence programs. Drug-dependency sleep disturbance can be influential (see Kay 1975a, 1975b; Hemmeter et al. 1993), because the coexistence of sleep disturbance and psychopathology is well known (Coursey et al. 1975; Kales et al. 1976; Monroe 1967). Recently, a longitudinal study showed that if sleep disturbances resolve, the risk of a new major depression is reduced (Ford and Kamerow 1989). Similarly, persistent drug-dependency insomnia may provoke heroin relapses during methadone maintenance. The present study aimed to provide further information on sleep of methadone and naltrexone patients. This is of special interest, because it is known that opioid-dopamine

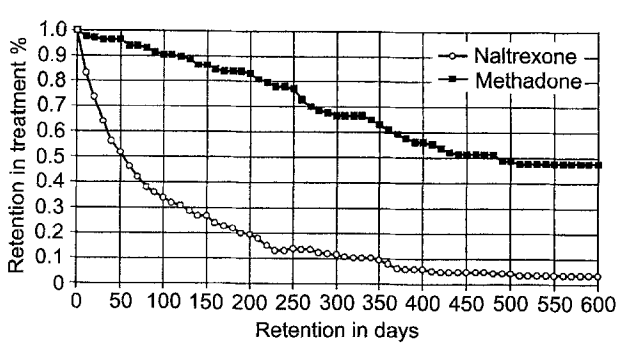

Fig. 1 Retention in treatment: naltrexone (n = 239); methadone (n = 182)

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interactions play a role in stress-induced insomnia (Fratta et al. 1987) and in the modulation of small movements during sleep (Henning et al. 1986; Staedt et al. 1995).

Subjects and methods

Patients

We compared 10 outpatients of our methadone project and 10 outpatients of our naltrexone treatment project. Due to the different addiction times of both cohorts a randomised assignment was not possible. Neurological and medical workup, including routine blood laboratory tests, revealed no severe abnormalities.

Controls

The control group consisted of 10 healthy students. Organic sleep disturbances had been excluded by sleep polygraphy (For further information about patients and controls see Table 1.) Informed consent was obtained from patients and controls and the study was approved by the Ethics Committee of the Medical Faculty of the Georg August University in Göttingen (Germany).

All-night polysomnographic recording (PSG)

The use of alcohol was not allowed during the days of the sleep investigation, and caffeinated beverages were restricted to the morning. During the PSG a standard montage according to Rechtschaffen and Kales (1968) with central EEG, horizontal EOG, submental and anterior tibialis muscle EMG was used. An apnea syndrome was ruled out by a one-night recording of abdominal motion and oronasal flow in patients and controls. The sleep parameters were visually scored according to the standard criteria (Rechtschaffen and Kales 1968) by two independent experienced raters. Two types of microarousals (abrupt acceleration of the EEG frequency; duration 1–15 s) were scored. A series of three or more MAs occurring during total sleep time (TST) within a certain time limit (minimum interval 5 s and maximum interval 2.5 min) was summarised to clusters. This summing up over TST allows a quantification of the cluster-disturbed sleep (CDS) in minutes (see Staedt et al. 1993). Because of the high interindividual variation in the sleep-stage distribution (Merica and Gaillard 1985) and age-related loss of deep sleep (Blois et al. 1983), we restricted group comparisons to sleep stages I and II, stage REM and slow-wave sleep. Self-reports about sleep quality were not performed, because insomniacs somehow misperceive their own state of consciousness (Carskadon et al. 1976). As an indicator for psychophysiological impairment the von Zerssen "Depression Skala" (D-S) and the von Zerssen "Befindlichkeits Skala" (Bf-S) (von Zerssen and Koeller 1976) was taken. The D-S scale is a subjective anxiety/depression symptoms rating of 16 items. The Bf-S scale is a subjective emotional distress symptoms rating of 28 items. The threshold for pathological value of the scales corresponds to the 88% percentile. All data for sleep variables and scores were expressed as mean ± 1 SD. The obtained data were compared by Wilcoxon rank sum test.

Results

The methadone group showed a significant reduction in cluster-disturbed sleep (CDS) as compared with naltrexone and controls (methadone 12.6 min, naltrexone 35.5 min, controls 31.3 min; Table 2). The MA frequency in CDS showed no significant difference between the control and patient groups (methadone 1.10/min, naltrexone 1.04/min, controls 1.40/min; Table 2). In addition, the cluster number and the cluster duration of methadone patients was shortened significantly as compared with naltrexone and controls (cluster number: methadone 3.2, naltrexone 8.7, controls 7.6; cluster duration: methadone 3.17 min, naltrexone 4.29 min, controls 4.10 min; Table 2). Compared with the methadone group in the naltrexone group MAs occurred in REM more often combined with an increase in anterior tibialis muscle EMG (duration 1–15 s), (number of arousal-related increases in muscle tone per hour: methadone 1.93/h, naltrexone 8.6/h, Fig. 2).

The group comparisons of classical sleep parameters (total sleep time = TST; light sleep = S1, S2; slow-wave sleep = SWS; rapid-eye-movement sleep = REM; time awake after sleep onset = wake; sleep latency = SL) re-

Table 1 Clinical data of patients and controls (± 1 SD) Levomethadone = effective enantiomer of D, L-methadone. Asterix means not present

	Methadone (n = 10)	Naltrexone (n = 10)	Controls (n = 10)
Gender	F = 3, M = 7	M = 10	M = 10
Age (years; mean)	36.6 ± 4.35	30 ± 5.04	26 ± 4
Unemployed	3	5	*
Heroin dependence (years; mean)	18	7	*
Levomethadone treatment (months)	33 ± 13.37	*	*
Levomethadone (dose, mg/day)	47	*	*
Naltrexone treatment (mean, months)	*	10 ± 9.75	*
Naltrexone (dose, mg/day)	*	50	*
Positive urine test Benzodiazepines	2	*	*
Positive urine test Cannabinoids	3	4	*
Positive urine test Cocaine	1	*	*

Table 2 Naltrexone/methadone/control group comparison of sleep microstructure parameters. Data are mean ± 1 SD. Asterisks indicate statistical significance (Wilcoxon; $P < 0.01$, $P < 0.001$)

	Methadone (n = 10)	Naltrexone (n = 10)	Controls (n = 10)
Cluster number	3.2* ± 2.99	8.7 ± 3.79	7.6 ± 2.01
Cluster duration	3.17** ± 1.79 min	4.29 ± 0.88 min	4.10 ± 0.75 min
Cluster disturbed sleep (CDS)	12.60** ± 11.86 min	35.50 ± 16.78 min	31.30 ± 11.38 min
Microarousal frequency in CDS	1.10 ± 0.23 min	1.04 ± 0.23 min	1.4 ± 0.27 min

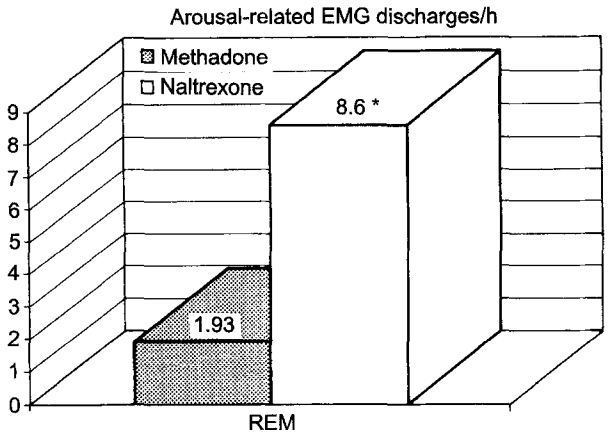

Fig. 2 Naltrexone/methadone group comparison of arousal-related increase in anterior tibialis muscle EMG in REM. Data are mean ± 1 SD. *Asterisks* indicate statistical significance (Wilcoxon; $P < 0.001$)

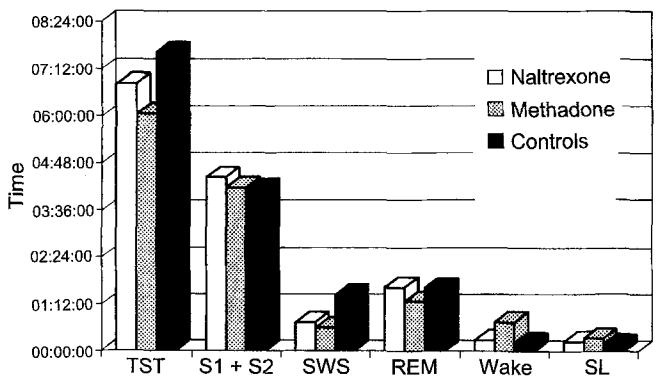

Fig. 3 Naltrexone/methadone/controls group comparison of classical sleep parameters (*TST* total sleep time; S1, S2 light sleep; *SWS* slow-wave sleep; *REM* rapid-eye-movement sleep; *Wake* time awake after sleep onset; *SL* sleep latency). (Because of the high interindividual and age-related changes in classical sleep parameters, statistical comparisons were not done

vealed noticeable differences regarding SL (methadone 19.59 ± 12.19 min, naltrexone 15.04 ± 6.50 min, controls 13.3 ± 9.53 min), TST (methadone 363.36 ± 56.2 min, naltrexone 409.36 ± 61.80 min, controls 457.0 ± 63.0 min), SWS (methadone 35.51 ± 34.48 min, naltrexone 44.39 ± 22.04 min, controls 86.51 ± 22.04 min), REM (methadone 76.10 ± 20.31 min, naltrexone 98.24 ± 41.57 min, controls 96.65 ± 15.85 min) and wake (methadone 45.02 ± 6.04 min, naltrexone 17.30 ± 15.55 min, controls 13.16 ± 10.46; Fig. 3). The assessment of the psychophysiological impairment revealed a significantly elevated D-S scale in methadone patients as compared with naltrexone patients, 83.67 percentile and 50.63 percentile in the latter (Fig. 4). In addition, methadone patients showed more subjective emotional distress in Bf-S scale as compared with naltrexone patients (68.25 percentile to 47.17 percentile; Fig. 4).

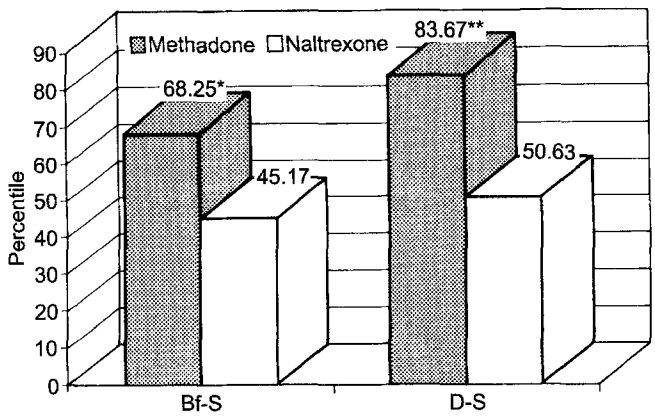

Fig. 4 Naltrexone/methadone group comparison of self-rating scales as an indicator for psychophysiological impairment: *D-S* scale von Zerssen "Depression Skala" (for anxiety-depression symptoms); *Bf-S* scale von Zerssen "Befindlichkeits Skala" (for emotional distress symptoms; for further information see von Zerssen and Koeller 1976; Wilcoxon; $P < 0.005$, $P < 0.005$)

Discussion

This is the first study which compares the effects of methadone and naltrexone on sleep induction and maintenance in addicts. Atypical effects on sleep by other abused drugs can be neglected, because additional abuse of drugs occurred in both groups (see Table 1) and is "usually" expected (Olesen et al. 1995). Because the previous literature described a slowing of wake and sleep EEG due to methadone administration (Isbell et al. 1948; Kay 1975b; Roubicek et al. 1969), we quantified microstructure alterations of sleep by our cluster arousal analysis (CDS). In detail CDS analysis allows the quantification of sleep parts which are influenced by abrupt accelerations of the EEG frequency (MA). With methadone we found a significant reduction in CDS as compared with both other groups, whereas the MA frequency remained stable in all three groups (Table 2). The reduction in CDS confirms the literature cited above (Isbell et al. 1948; Kay 1975b; Roubicek et al. 1969). The MA frequency stability may reflect "normal" oscillations in the balance of inhibitory and excitatory neuronal systems during sleep, which are involved in sequence of Non-REM/REM generation (McGinty 1982). Under this assumption methadone's "abnormal reduction" of CDS could alter MA-triggered periodically recurrent Non-REM/REM oscillations, thus leading to the observed disruption in sleep continuity with an increase in wakefulness (Fig. 3). Besides the methadone-induced lethargy and decreased motivation (Martin et al. 1973), the observed high level of depressive symptoms in D-S scale (Fig. 4) of methadone patients may reflect the well-known coexistence between sleep disturbances and depressive symptoms (Coursey et al. 1975; Ford and Kamerow 1989; Kales et al. 1976; Monroe 1967). Additionally, the increased subjective emotional distress (Bf-S scale; Fig. 4) of methadone patients can be related to the sleep fragmentation, because it is known that experimental NonREM sleep fragmenta-

tion induces symptoms such as irritability, loss of appetite and unusual somatic fatigue syndrome (Agnew et al. 1967; Moldofsky et al. 1975). Concerning drug-induced sleep disturbance and depression and the coexistence of depression and drug misuse (for an overview see Magruder-Habib et al. 1992), counterarguments focus on superimposed psychosocial factors such as unemployment and duration of addiction (Capone et al. 1986). Of course, in comparison to naltrexone, our methadone group had a longer duration of addiction.

However, on the other hand, only 3 of 10 methadone compared with 5 of 10 naltrexone patients were unemployed. In addition, Rounsaville et al. (1986) found a marked reduction in depressive symptomatology in opiate addicts following treatment for drug misuse. Taking into account the "normal" D-S ratings and the compact TST (Figs. 3 and 4), in our naltrexone group, we believe that depression in methadone patients can be related to the observed sleep disturbances.

The high standard deviation of the classical sleep parameters, e.g. TST in patients and control TST (methadone 363.36 ± 56.2 min, naltrexone 409.36 ± 61.80 min, controls 457.0 ± 63.0 min) is in accordance with the data of Merica and Gaillard (1986). But the short SL (15.04 ± 6.5 min) and the "normal" TST (409 ± 61.80 min) in naltrexone patients as compared with controls and methadone patients are surprising. Together with the animal data of Fratta et al. 1987 (they found that opioid antagonists and dopamine D1 antagonists, but neither diazepam nor opioids, reduced the sleep latency in sleep-deprived rats) these results indicate that opioid-dopamine interactions are involved in the regulation of sleep. In contrast to the compact TST in naltrexone patients, we observed a marked REM sleep alteration by an arousal-related increase in anterior tibialis muscle EMG (Fig. 2). The occurrence of these EMG activations in naltrexone is not surprising because opioids as well as opioid antagonists modulate the dopaminergic transmission (Chesselet et al. 1983; De Vries et al. 1993; Di Chiara and Imperato 1988) and the involvement of the latter system in the sleep-stage-dependent modulation of movements is also known (Segawa and Nomura 1991; Staedt et al. 1995 a, b).

In summary, our findings indicate that drug-dependency sleep disturbance in methadone-treated addicts may be a contributor towards depression, which may increase the risk of heroin relapse or cocaine abuse and therefore drug-related death. The positive effects of naltrexone on sleep points to an involvement of the opioid-dopamine interaction in sleep. However, whether the therapeutical effect of naltrexone on sleep is also present during the acute detoxification phase (3–5 weeks after starting the withdrawal) when the drop out rate is high cannot be decided on the basis of the results of our long-term treatment period.

In conclusion, the validity of our results is limited by the small number of patients and the lacking randomised assignment. Finally, further prospective studies with larger groups of patients should include sleep polygraphic recordings to evaluate special strategies for drug-dependency sleep disturbances.

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