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IV. Quantitative Sleep EEG Findings

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Classification of Psychotropic Drugs Based on Digital Computer Sleep Prints[1]

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Introduction

Previous investigations have shown that psychotropic drugs can be classified based on qualitative and quantitative evaluation of the awake spontaneous brain function and evoked brain activity [4, 15, 16, 25, 27, 61, 62, 64]. The fact that bioelectrical classification turned out to be very similar to clinical classification can be explained inasmuch as drug-induced alterations in behavior are the result of drug-induced chemical changes in the brain. Although the sleep EEG could be used as another tool in the armamentarium of psychopharmacology to objectively determine the mode of action of psychotropic agents, and despite the fact that many drugs are increasingly taken at bedtime, the practical application of this technique in psychopharmacology remains scarce. This is largely due to the great amount of time involved in the visual evaluation of an all-night sleep record. However, the utilization of a computerized graphic display of the all-night sleep profile in the form of a digital computer 'sleep print' [31, 32] has greatly alleviated this problem. Using this method, we have systematically studied the effects of a series of minor and major tranquilizers on the all-night sleep process. This chapter attempts to present a survey of this work and to deal with the question of whether or not it is possible to classify psychotropic agents based on quantitative sleep parameters.

1 Supported, in part, by USPHS grant MH-11381 and the International Association for Psychiatric Research.

Methodological Aspects

Anxiolytic and hypnotic drugs were administered predominantly in single oral doses to normal healthy volunteers and included flurazepam (30 mg), methaqualone (300 mg), U-31,889 (a newly developed triazolobenzodiazepine in doses of 0.5, 1.0 and 2.0 mg), triazolam (U-33,030) (another new benzodiazepine derivate in doses of 0.1, 0.5 and 1.0 mg), clorazepate dipotassium (7.5 mg three times a day), and diazepam (5 mg three times a day). Active drugs and placebo were given at bedtime in 3- to 6-day intervals on a randomized basis.

Neuroleptics were studied after administration of single doses (35 and 60 mg chlorpromazine, 10 mg butaperazine) in normals and schizophrenics as well as during long-term drug treatment in schizophrenic populations. In the latter, all-night sleep recordings were carried out after 2 months of placebo administration as well as during the first month of drug treatment (with a mean daily dosage of 24 mg thiothixene, 26 mg fluphenazine, 10 mg haloperidol, 35 mg molindone, or 392 mg thioridazine) and during the third month of drug therapy (with a mean daily dosage of 65 mg thiothixene, 69 mg fluphenazine, 15 mg haloperidol, 126 mg molindone, or 800 mg thioridazine). The dosages and types of application of representatives of other psychopharmacological classes will be described in their respective sections.

The all-night sleep EEG was recorded between 9.30 p.m. and 6.00 a.m. using a Grass Model 6 electroencephalograph. The right occipital to anterior vertex EEG lead was recorded on tape (Ampex FR 1300) and analyzed off- or on-line based on period analysis [6] using digital computer (IBM 1620/1710 and PDP-12) programs [65, 66]. This program permits analysis of the primary wave (zero cross) and its first derivative in 30-sec epochs at a sampling rate of 320 points/sec and provides 20–22 EEG measurements (average frequency, average frequency deviation, and 8 frequency bands for the primary wave and first derivative as well as the average absolute amplitude and amplitude variability – Drohocki). Each 30-sec epoch is automatically classified into one stage of the 3-stage sleep classification (N = non sleep, LVF = low voltage fast sleep and SWS = slow wave spindle sleep), 5-stage sleep classification (W, 1, 2, 3, 4) [9] and 9-stage sleep classification (W = A – AB, 1 = B, 2 = BC – C, 3 = CD – D, 4 = DE – E) [32] based on seven or eight primary wave measurements (fig. 1). Based on these classifications, it is possible at the end of each sleep night to plot 'sleep prints' [31] which reflect the profile of an all-night sleep process (fig. 2) as well as to compute and plot the percentage of time spent in each sleep stage.

Heart rate, EMG, and horizontal and vertical eye movements were also monitored. The lengths of REM periods were evaluated visually based on a low voltage EEG pattern, the disappearance of muscle potential, and the appearance of rapid eye movement (REM). In addition, the number of REM cycles (REM periods), as well as the number of 30-sec samples with single REM or REM burst activity were evaluated from each record.

Results

Anxiolytic-Induced Changes

Digital computer sleep prints demonstrated that anxiolytics (minor tranquilizers) markedly alter the all-night sleep profile (fig. 3).

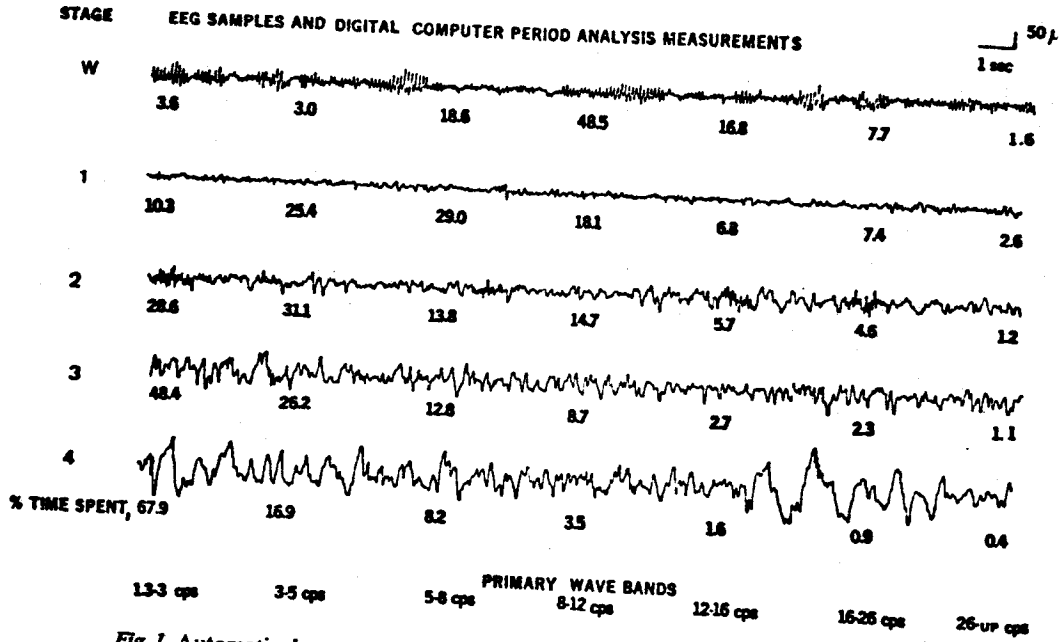

Fig. 1. Automatic sleep stage classification based on EEG digital computer period analysis. EEG samples and their corresponding digital computer period analysis measurements are demonstrated for each sleep stage (5-level sleep stage classifications), $O_2 \cdot Cz$. The automatic sleep stage classification is based on the frequency distribution in the eight primary wave bands.

Concerning *sleep stages*, generally a decrease of deep and increase of light sleep stages can be observed after administration of anxiolytics. Figure 4 demonstrates the effect of several anxiolytics on computer-classified sleep stages based on a comparison with placebo-induced changes. The differences are expressed in t-values which include both the mean change values as well as the variance. As can be seen, diazepam (5 mg three times a day) and clorazepate dipotassium (7.5 mg three times a day) significantly augmented computer-classified sleep stages B and BC but significantly attenuated C, CD, DE and E. U-31,889, a new benzodiazepine, in dosages of 1.0 and 2.0 mg, significantly decreased C and CD, while increasing AB. Thus, computer-classified sleep stage profiles of anxiolytics are generally characterized by an augmentation of light sleep stages (AB, B and BC), while deeper sleep stages are attenuated. It seems that these changes are due primarily to an increase in fast β-activity, which results in a shift of the classification toward light sleep stages, since the automatic sleep classification is based on frequency

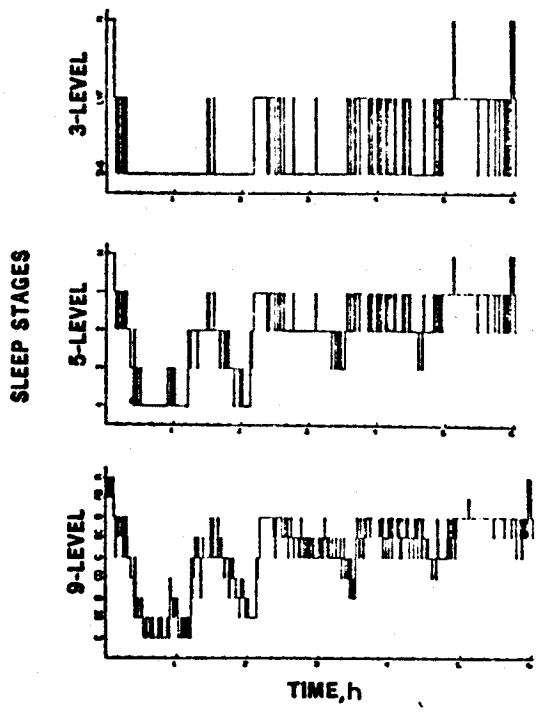

Fig. 2. M.P., male, 25 years, normal volunteer. Digital computer sleep stage prints playback of 4.12.71, placebo, T33 CH2 8–18 KF, 0.5–50 EEG 13244) based on the 3-, 5-, and 9-level sleep stage classification (automatically plotted classification derived from baseline cross-frequency patterns by EEG computer period analysis). Time in hours is shown in the abscissas and sleep stages based on different sleep stage classifications are represented in the ordinates. The top plot demonstrates the 3-stage classification. N = Neither; LVF = low voltage fast sleep; SWS = slow wave spindle sleep. The middle plot represents the 5-stage classification, according to DEMENT and KLEITMAN's [9] classification: W, 1, 2, 3 and 4. The bottom plot shows the 9-stage classification (A, AB, B, BC, C, CD, D, DE, E). While the 3-stage classification gives the most simple profile, the 9-stage classification demonstrates the most detailed sleep profile.

distribution, as is the visual classification. A decrease of deep sleep stages was also noted after single doses of 10 mg diazepam and was found to be associated with a beneficial effect on somnambulism and enuretic episodes [60].

Our findings confirm results of KALES *et al.* [41] using visual evaluation techniques, who reported a decrease of deep sleep stages after 50 mg chlordiazepoxide and 10 mg diazepam. FREEMON *et al.* [17] noted an increase in stage 2 after 1,200 mg meprobamate while 800 mg of this drug did not significantly influence sleep stages [69].

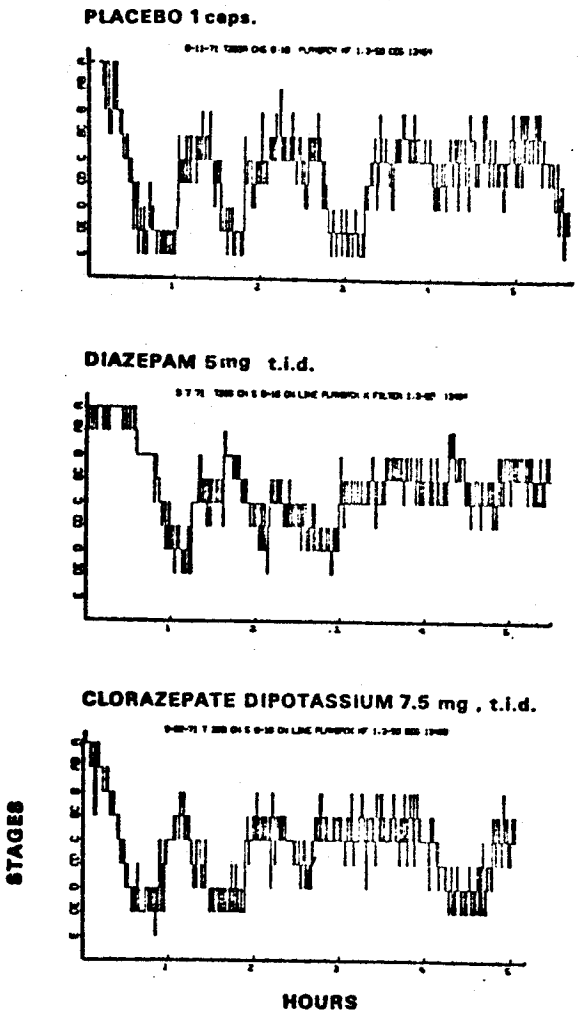

Fig. 3. L. M., 25 years, male normal volunteer. Digital computer sleep prints after oral administration of placebo, diazepam and clorazepate dipotassium. Time is indicated in the abscissas, stages in the ordinates. As can be seen, the anxiolytics (diazepam and clorazepate dipotassium) decrease deep sleep stages and increase light sleep stages.

When we compared changes in sleep stages after anxiolytics to those seen after hypnotic drugs, similar findings came to the fore (fig. 4). 300 mg methaqualone increased stages AB and B and decreased C, CD and E. Triazolam, a new triazolobenzodiazepine, significantly increased stage B and

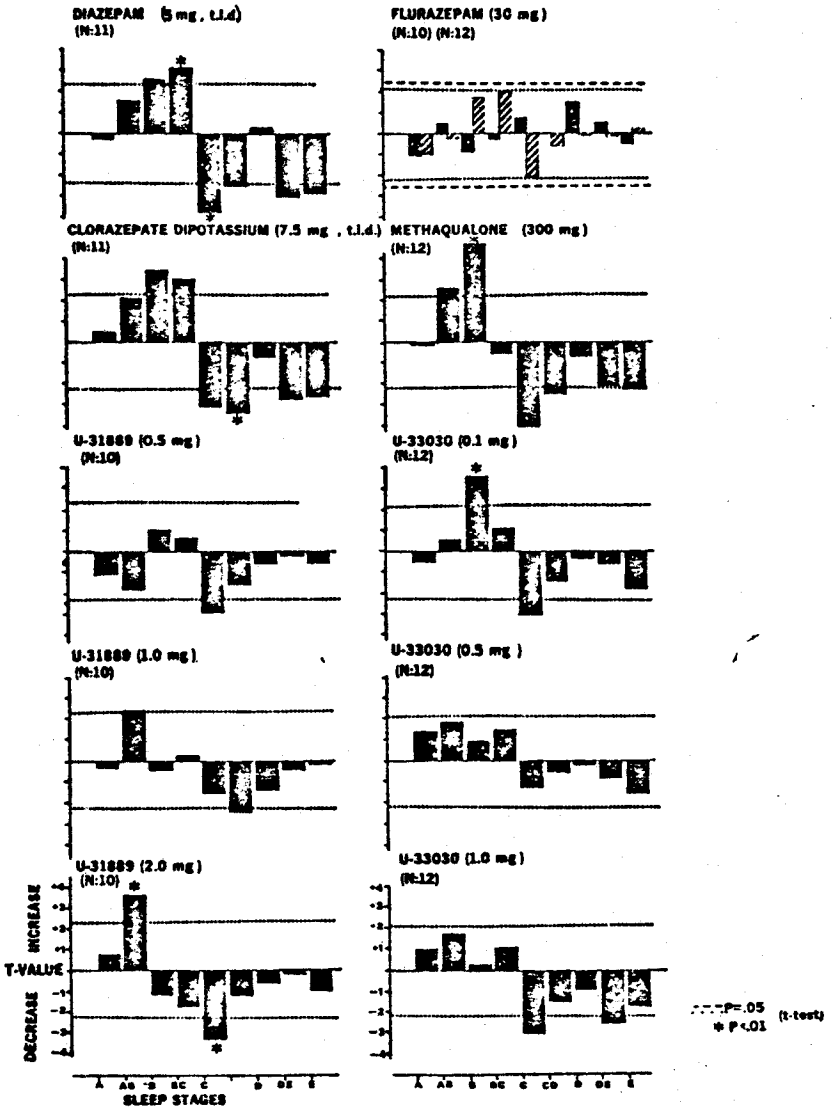

Fig. 4. Effects of anxiolytics and hypnotics on computer-classified sleep stages. Sleep stages are indicated in the abscissas; drug-induced changes as compared to placebo are expressed in terms of t-values (t-value is directly proportional to change value, inversely proportional to variance) and are represented in the ordinates. Anxiolytics generally decrease deep sleep stages and increase light sleep stages. Hypnotics induce similar alterations, with the exception of 0.5 mg triazolam and 30 mg flurazepam (in two different studies) which did not change the sleep profile at a level of statistical significance.

decreased stages C and DE in doses of 0.1 and 1.0 mg. However, 0.5 mg triazolam, as well as 30 mg flurazepam, did not induce any significant alterations in sleep stage distribution in two different studies. Interestingly, the latter two drugs were found to be the most effective ones in improving the quality of sleep based on sleep self-rating scales.

The literature concerning the influence of hypnotics on sleep stages is diverse. While some researchers report a decrease of deep sleep stages after hypnotics such as 500 mg glutethimide and 100 mg pentobarbital [42], 40 mg guanethidine [10], and 300 mg methaqualone [18], other researchers noted a hypnotic-induced augmentation of δ-sleep, as for instance after 500 mg α-chloralose [46, 70], 120 mg phenobarbital and 300 mg thiopental i.v. [46]. LESTER *et al.* [47] found that δ-sleep increased in the first half of the night after 200 mg secobarbital. An increase of sleep stage 2 was observed by HAIDER [20] and HAIDER and OSWALD [21] after 200 mg amylobarbitone and 10 mg nitrazepam, by WILLIAMS and AGNEW [69] after 200 mg pentobarbital, by KALES *et al.* [42] and GOLDSTEIN *et al.* [18] after 500 mg glutethimide. No significant effect on sleep stages was reported after 300 mg methaqualone by WILLIAMS and AGNEW [69], after 250 mg methaqualone by EVANS and OGUNREMI [12], after 150 and 300 mg methaqualone and 500 and 1,000 mg chlorahydrate by KALES *et al.* [43].

An anxiolytic- and hypnotic-induced decrease in deep sleep stages based on the EEG does not mean a decrease of the subjective experience of the depth of sleep [40]. Contrarily, a drug-induced decrease of deep sleep stages and increase of light sleep stages was correlated with a feeling of having spent more time in deep sleep and less time in light sleep than usual.

According to our investigations, the subjective experience of an augmented deep sleep can be correlated with an increase in fast activity, which in turn leads to greater 'hangover' side effects in the morning. This suggests that anxiolytic- or hypnotic-incuded sleep, particularly after the administration of higher dosages, closely resembles 'anaesthetic' or 'narcotic' sleep as seen after some barbiturates. An 'ideal' hypnotic, however, produces long lasting fast activity in the EEG in a smaller quantity and thus does not significantly attenuate deep sleep stages (stages DE and E or 4). Indeed, we have discovered recently that those sleeping pills which are regarded as the best by the subjects themselves, such as 30 mg flurazepam and 0.5 mg triazolam, produce no statistically significant changes at all in sleep stages.

Evaluation of *REM characteristics* after administration of the aforementioned anxiolytics in our sleep laboratories demonstrated an attenuation in REM activity (fig. 5). However, classical anxiolytics such as diazepam and

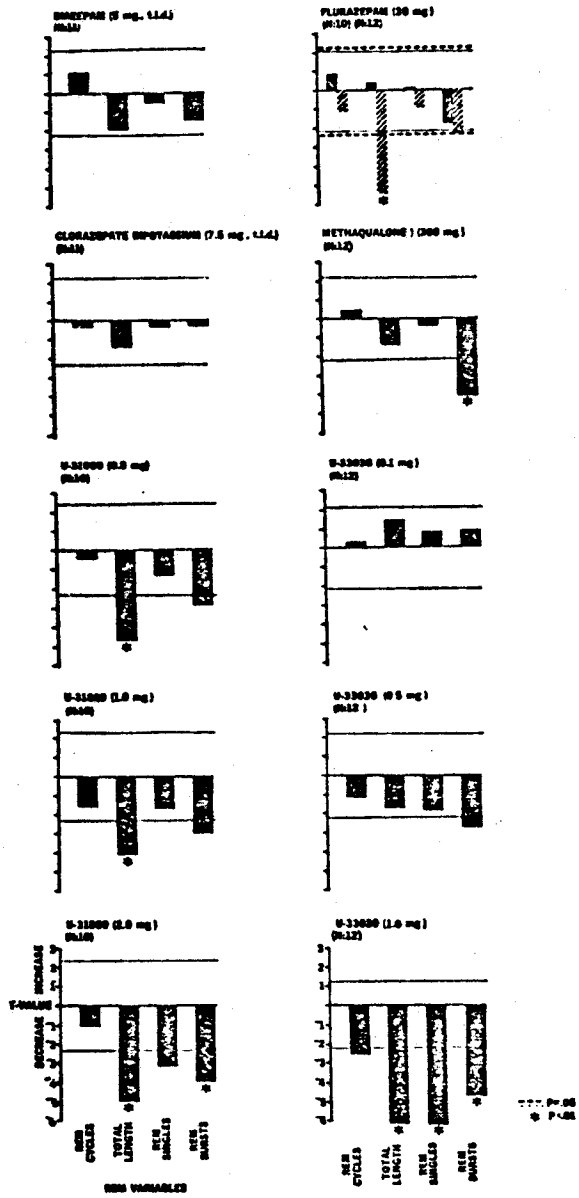

Fig. 5. Effects of anxiolytics and hypnotics on visually evaluated REM activity. REM variables (REM cycles, total length of REM periods, epochs with single REM, epochs with REM bursts) are indicated in the abscissas; drug-induced changes as expressed in t-values are indicated in the ordinates. Both minor tranquilizers and hypnotics suppress REM activity.

clorazepate dipotassium did not decrease any REM variables at a level of statistical significance, whereas classical hypnotics such as flurazepam and methaqualone did (fig. 5). If one speculates that the marked decrease of REM activity, along with other characteristics, may be indicative of hypnotic drugs, one would predict that higher dosages of U-31,889 and triazolam would act as hypnotics, while lower dosages might be anxiolytic. Clinical studies seem to support this prediction.

As did we in our studies, KALES *et al.*[41] could not find a significant suppression of REM with diazepam (10 mg) as well as chlordiazepoxide (50 mg). FREEMON *et al.*[17] described a decrease of REM sleep after 1,200 mg meprobamate. Our findings of suppressed REM activity after administration of hypnotics are in agreement with those of many investigators. A decrease of REM sleep was observed after 10–15 mg nitrazepam as well as 200–400 mg amylobarbitone [11,20,21,51], 400 mg heptabarbitone [52], 100–200 mg pentobarbital [3,23,69], 300 mg thiopental i.v.[46], 500 mg α-chloralose [46, 70], 800 mg chloralhydrate [12], 200 mg phenobarbital [13], 100 mg quinalbarbital and 100 mg amylobarbital [8], 60 mg flurazepam, 300 mg methaqualone and 300 mg methyprylon [42,43], and 500–1,000 mg glutethimide [42, 56,69].

Neuroleptic-Induced Changes

Single Dose Trials

Single dose trials in 11 normal healthy volunteers demonstrated that 35 mg chlorpromazine shortens the onset of sleep, decreases light sleep and increases δ-sleep (fig. 6). REM activity significantly increased.

Different single doses administered to a schizophrenic had different effects on the sleep prints. While no significant changes were seen after 10 mg chlorpromazine, 25 mg increased the variability of sleep cycles [28]. After 60 mg, the maximal sleep depth shifted from early night to early morning hours; light sleep stages (AB + B) and stages DE + E decreased significantly, while middle deep sleep stages were augmented. Investigations with piperazine phenothiazines (10 mg butaperazine and 10 mg stelazine) in the same subjects demonstrated an attenuation of deep sleep stages. The length of REM periods, REM cycles and number of epochs with single REM and REM burst all decreased after 60 mg chlorpromazine and 10 mg butaperazine, while 10 mg stelazine increased the amount of REM activity as compared with the placebo nights.

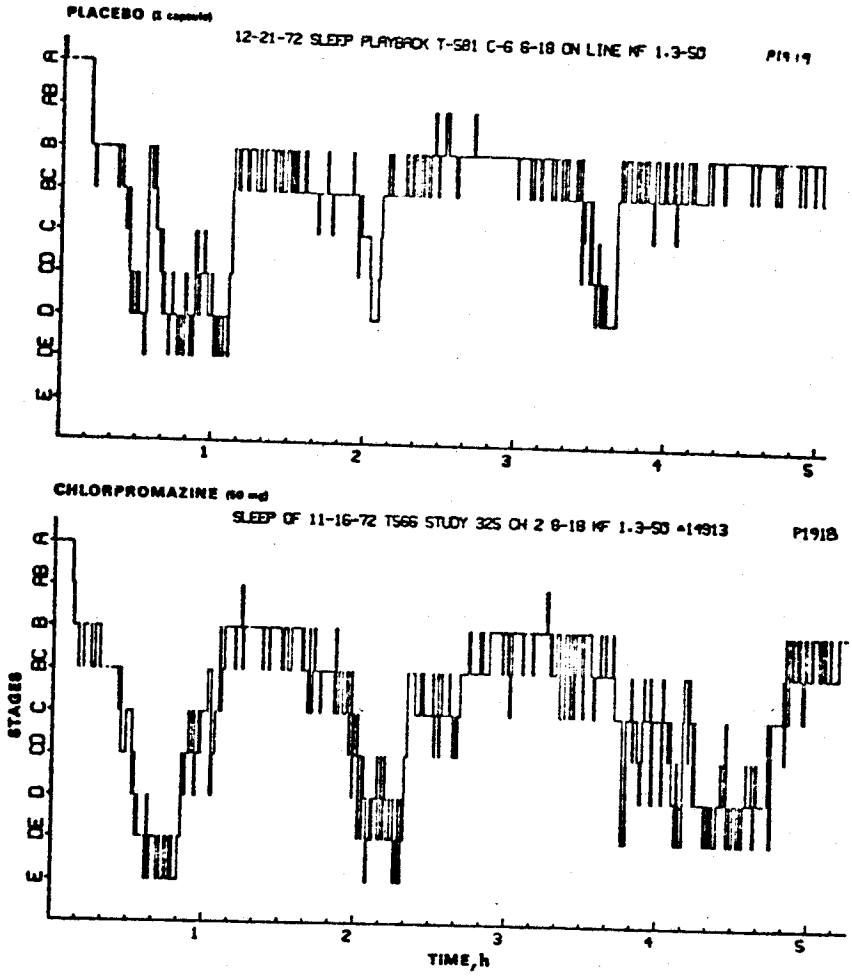

Fig. 6. G. McC., male, 27 years, normal volunteer. Effects of 50 mg chlorpromazine on the sleep profile expressed in digital computer sleep prints (after oral administration of one single dose at bedtime). Time is shown in the abscissas, stages in the ordinates. 50 mg chlorpromazine shortens the onset of sleep, increases deep sleep stages and decreases awakenings and light sleep.

Multiple Dose Trials

Multiple dose trials were carried out in chronic schizophrenics over a period of 3 months. Regarding computer-classified *sleep stages*, chronic administration of thiothixene in doses of 25 mg daily increased stage AB, while in doses of 65 mg it increased deep sleep stages D, DE and E (fig. 7). Fluphenazine hydrochloride did not induce any significant changes in low

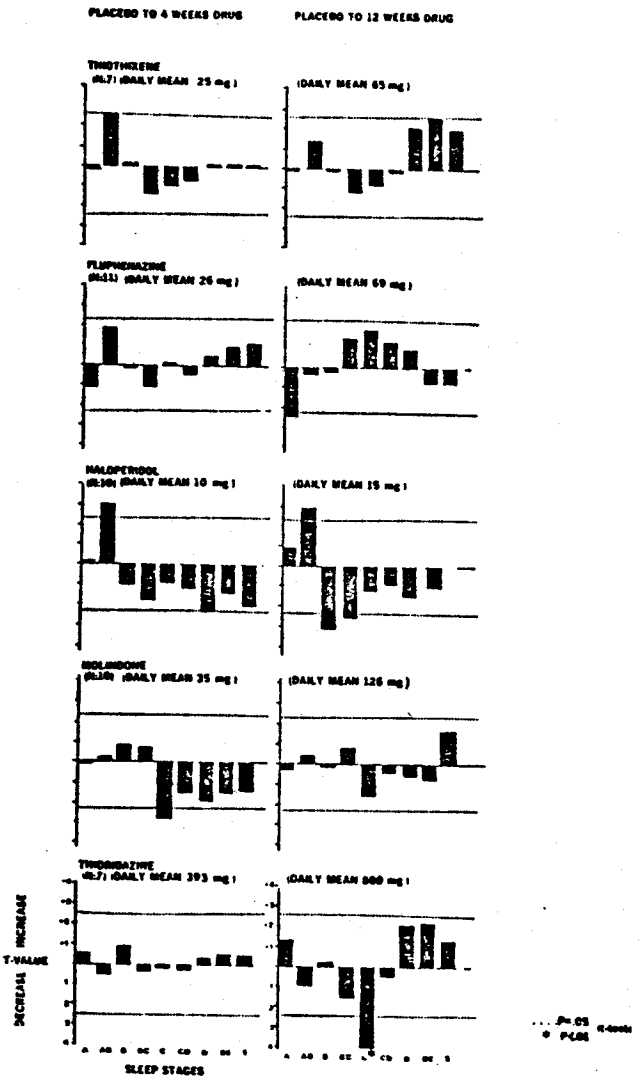

Fig. 7. Effects of neuroleptics on computer classified sleep stages. Sleep stages are represented in the abscissas, drug-induced changes as compared with placebo are expressed in t-values and are indicated in the ordinates. While thiothixene in lower dosages increased stage AB, it increased deep sleep stages in higher dosages. In higher dosages fluphenazine decreased stage A. Haloperidol increased stage AB and decreased deep sleep stages in both low and high dosages. Molindone decreased deep sleep stages in the low dosage range and showed a trend towards an augmentation of stage E in the higher dosage range. Thioridazine did not significantly influence the sleep profile in lower dosages, while in higher dosages it significantly attenuated middle deep sleep stages and augmented deep sleep stages.

doses (25 mg); in high doses (70 mg), a significant decrease in stage A occurred together with a trend toward an augmentation of stages DC, C and CD (fig. 7). Haloperidol in doses of 10 and 50 mg increased stages AB and decreased stages B, BC and D (fig. 7). Molindone in doses of 35 mg produced a decrease in stage C, but no significant alterations occurred in the higher dosage range (126 mg) (fig. 7). Thioridazine, in doses of 393 mg daily, did not induce any significant changes; 800 mg significantly attenuated stage C, while stages D, DE and E tended to be augmented (fig. 7).

Our observations regarding some consistency of drug-induced changes in computer-classified sleep stages after anxiolytics and hypnotics could not be paralleled with neuroleptic agents. This might be due to the fact that our populations consisted of chronic schizophrenics who, as is known, have highly variable sleep patterns [39, 58, 59]. Interestingly, in lower dosages, haloperidol and molindone decreased very deep sleep stages, while in higher dosages thiothixene, molindone and thioridazine increased stage E (stage 4) sleep.

The high inconsistency of findings regarding changes in sleep stages after administration of major tranquilizers is reflected also in the literature. LESTER and GUERRERO-FIGUEROA [46] reported an increase of δ-sleep with 100 mg chlorpromazine, while no effects in sleep stages were reported after doses of 0.4 g/kg [57], after 150 mg [48] and 100 mg chlorpromazine [45], although the latter authors found the total sleep time increased. COULTER *et al.* [7] described decreased δ-sleep one day after 1 mg reserpine administration.

Regarding visually evaluated *REM activity*, thiothixene chronically administered in doses of 24 mg daily, significantly increased single REM, while 65 mg did not significantly alter the REM variables (fig. 8). Fluphenazine in daily doses of 26 mg induced an increase in all REM variables, reaching a level of statistical significance in REM cycles. In higher doses (69 mg), however, there were no significant alterations (fig. 8). Haloperidol in doses of 10 mg significantly increased REM bursts, although in doses of 15 mg it significantly decreased the number of REM cycles, while significantly increasing single REM (fig. 8). Molindone in doses of 35 and 126 mg daily did not alter any REM variables (fig. 8). Thioridazine in doses of 392 mg increased the total REM activity, reaching a level of statistical significance in the total length of REM sleep as well as in REM bursts (fig. 8). With higher dosages (800 mg), the changes went in the same direction, but were not statistically significant.

Based on our findings involving long-term drug treatment of chronic schizophrenics, one can conclude that neuroleptics augment REM activity, particularly REM bursts and single REM. Higher dosages seem to produce

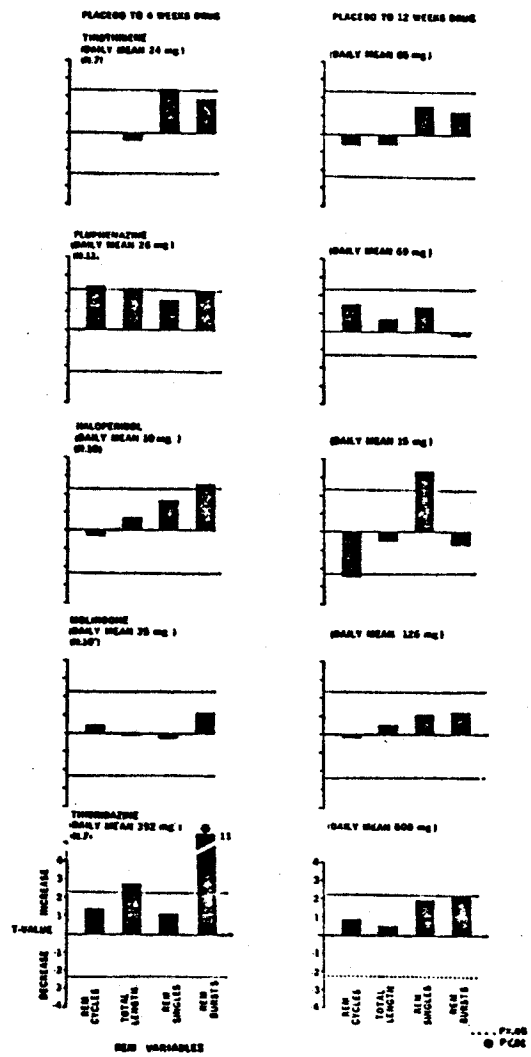

Fig. 8 Effects of neuroleptics on visually evaluated REM activity. REM variables are represented in the abscissas; drug-induced changes are expressed in t-values and are indicated in the ordinates. Generally, neuroleptics increased REM activity, which in several variables and in several drugs reached a level of statistical significance.

fewer changes (except haloperidol) than lower dosages. An increase of REM sleep was reported with 25 mg [49] and 50 mg chlorpromazine [67], while a decrease was noted with 100 mg [49] and 200 mg chlorpromazine [13]. WILLIAMS *et al.* [70], HARTMANN [22] and HOFFMAN and DOMINO [24] described an increase of REM activity after 1, 2 and 0.14 mg/kg reserpine, respectively. COULTER *et al.* [7] also found increased REM sleep with 1 mg reserpine one day after medication.

Antidepressant-Induced Changes

Both imipramine (35 mg) and amitriptyline (35 mg) administered in a normal volunteer induced an increase of deep sleep stages as compared with placebo (fig. 9), while REM activity was suppressed. This is in agreement with ZUNG's [73, 74] findings, who described increased δ-sleep and attenuated REM sleep with 75 mg desipramine in normal and depressed subjects. RITVO *et al.* [55] reported an increase in stage 2 and decrease in REM after 50 mg imipramine in enuretic patients. HARTMANN [23] found decreased REM sleep in normals with 75 mg amitriptyline. BREBBIA *et al.* [5] could not find significant alterations in sleep stages of a mixed population after 1 g/24 h lithium, while KUPFER *et al.* [44] reported increased δ-sleep and decreased REM activity in manic-depressive patients treated with 1.8 g/24 h lithium. Wyatt *et al.* [71, 72] noted decreased REM, but no effects on sleep stages of depressed and normal subjects after the administration of several MAO inhibitors (400 mg isoniazid, 60 mg isocarboxazid, 15 mg mebanazine, 45 mg phenelzine, 60 mg phenelzine and 100 mg pargyline). AKINDELE *et al.* [1] observed an increase in slow wave spindle sleep and decrease in REM sleep with 90 mg phenelzine in normals and depressed patients, while no effect on sleep stages after 10 mg/kg nialimide.

Hallucinogenic Drug-Induced Changes

Hallucinogenic compounds, such as 50 μg LSD-25, 2 mg cyclazocine and 1 mg ditran, markedly prolonged sleep latency, significantly decreased deep sleep stages (C-E) and significantly increased awakening stages (fig. 10). The length of REM time, the number of REM cycles, as well as the number of epochs with single REM and REM burst, were significantly attenuated with the two former drugs, while changes after ditran did not reach a level

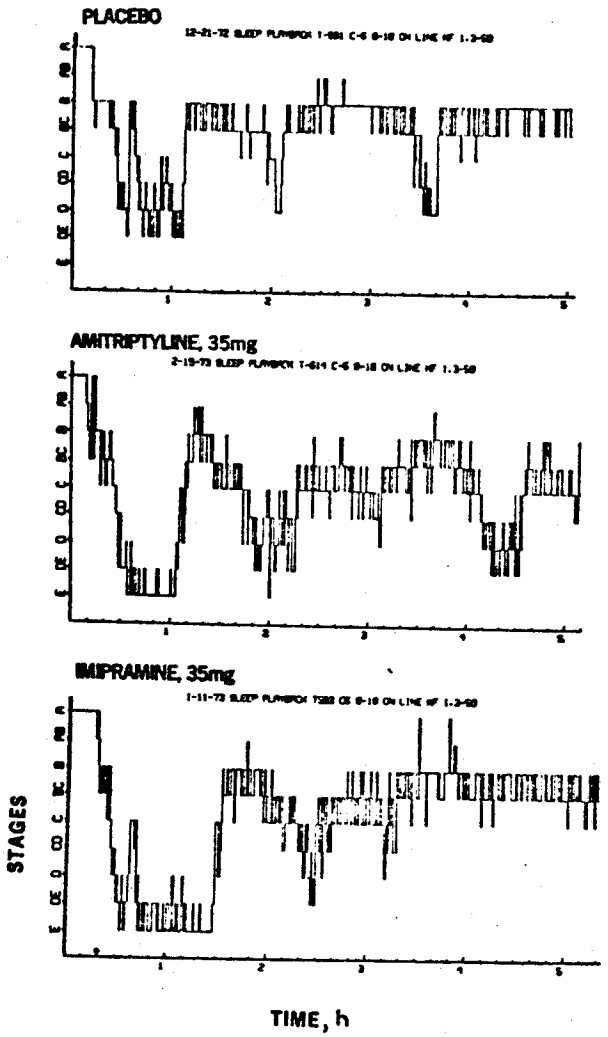

Fig. 9. G.McC., male, 27 years, normal volunteer. Effects of tricyclic antidepressants on digital computer sleep prints. Time is represented in the abscissas, sleep stages in the ordinates. Tricyclic antidepressants increased awake and deep sleep stages and decreased stage B.

of statistical significance. 1 mg atropine significantly decreased stages C, DE, and E, as well as the number of REM cycles.

When we chronically administered 2 mg cyclazocine daily to a depressive patient because of the drug's antidepressant properties, stages D, DE and E decreased at the beginning of the treatment, while after 3 weeks of treatment

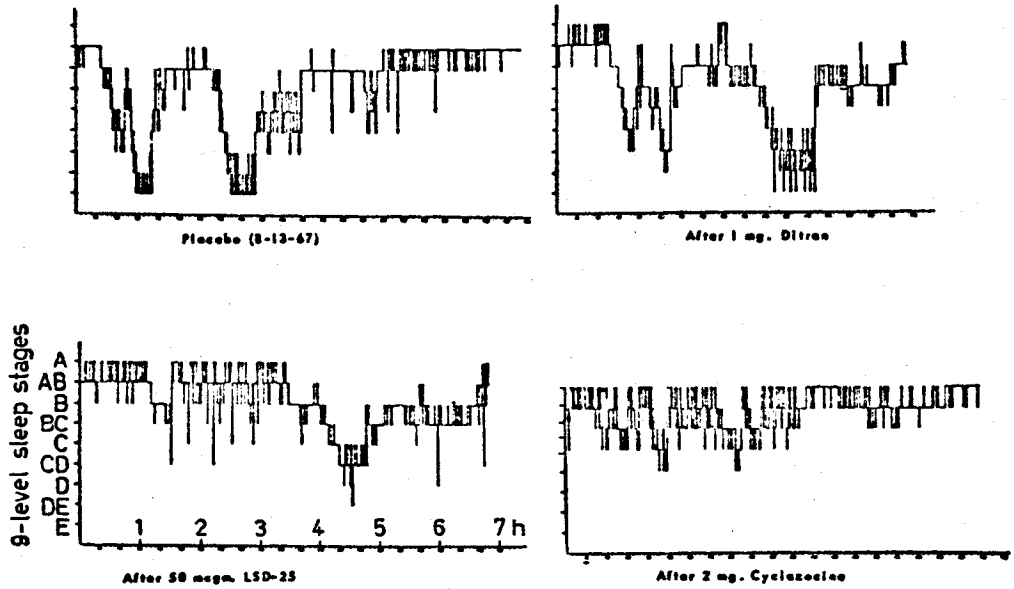

Fig. 10. J.B., 28 years. Effect of hallucinogenic drugs on sleep prints (based on computer period analysis of EEG). Time is represented in the abscissas, sleep stages in the ordinates. Hallucinogenic compounds such as 1 mg ditran, 50 mg LSD-25 and 2 mg cyclazocine delayed the onset of sleep, increased awakening stages and decreased deep sleep stages.

stage E increased significantly (table I). Stage AB was augmented throughout the treatment, while there was a significant attenuation of the length of REM periods, as well as the number of REM cycles and single REM and REM burst activity.

GREEN [19] described increased REM sleep after 300 μg LSD in one alcoholic patient and MUZIO *et al.* [50] described increased REM during the first part of the night in 12 normals after 30 μg LSD. TOYODA *et al.* [68] found that 10 mg atropine did not affect sleep stages. SHAGALES *et al.* [57] described a decreased REM sleep in normals after 0.006 mg/kg scopolamine.

Stimulant-Induced Changes

10 mg dextroamphetamine significantly decreased stages D, DE and E, while stage A and the length of REM periods were found to be increased. Such alterations were also described in the literature as being typical for

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Table I. Effect of cyclazocine treatment on sleep stages and on REM, drug nights (7) versus placebo nights (5)

Drug nights (7) versus placebo nights (5)	Sleep stages																	REM		
	9-level								5-level					3-level				number of periods	burst	single
	A	A–B	B	B–C	C	C–D	D	D–E	E	A	B	C	D	E	N	LVF	SWS	length of periods		
November 6, 1967, 2 mg		++	++				−−	−−			++	++		−−	++	++	−−		−−	
November 7, 1967, 2 mg		++		+	+	−	−−	−−			++			−−	−−		−−		−−	
November 8, 1967, 2 mg					++		−−	−−	−				++	−−	−				−−	
November 9, 1967, 2 mg		++	−	−−	++	++		−−	−				++	−−					−−	
November 10, 1967, 2 mg	++	++	−	−−	++	++	+	−		+	−	+	++	−−	++	−			−−	
November 16, 1967, 2 mg		++		−	++	+	−			++	−		++		++	−			−−	
November 21, 1967, 2 mg	++	++		−−			−−	−−	++	++		+	+				−		−−	

G. R., age 25 years. Dx: Depression.
+ = Increase at 0.05 level or better (t-test); ++ = increase at 0.01 level or better; − = decrease at 0.05 level or better; −− = decrease at 0.01 level or better.

stimulatory compounds. RECHTSCHAFFEN and MARON [54] reported a decrease of total sleep time and REM after 15 mg amphetamine in 8 normals. BAEKELAND [2,3] noted a decrease of REM after 5 mg methylphenidate and 15 mg amphetamine and an increase of stage 2 after the latter drug.

Conclusion and Summary

Previous investigations involving visual (eyeball) evaluation of the awake (resting) EEG have suggested that drugs therapeutically effective in schizophrenia (major tranquilizers or neuroleptics), in anxiety syndromes (minor tranquilizers or anxiolytics), and in depressive patients (antidepressants or thymoleptics) produce different EEG patterns whether administered in single dosages or chronically [4, 14–16, 25, 26]. Based on digital computer analysis of the awake EEG and somatosensory evoked potentials, we could not only confirm these previous findings but could also predict the type of psychotropic activities of newly developed drugs [27, 29, 63]. In order to answer a further question, whether psychotropic drugs with different clinical effects produce significant alterations on sleep EEG and REM parameters, we have in recent years carried out a series of studies in normal volunteers and hospitalized patients after single and multiple dosages of psychotropic drugs [30, 33–38, 40, 53]. The results of our studies indicate the following.

(1) The anxiolytic drugs significantly decrease deep sleep stages and increase light sleep stages. They also tend to decrease the length of REM periods, as well as the amounts of REM bursts and single REM activity. The hypnotic drugs tend also to produce similar alterations in sleep stages and REM activity. However, the 'good' hypnotics attenuate deep sleep stages to a lesser degree and decrease REM activity (particularly REM bursts) much more than 'classical' anxiolytics.

(2) The major tranquilizers, particularly haloperidol and molindone in lower daily dosages, decrease slow wave spindle sleep. In higher dosages, however, thiothixene, molindone, trifluoperazine, and thioridazine markedly increase stage 4 sleep. Most of the REM characteristics, but particularly REM burst activity, increased during daily administration of low dosages of thiothixene, fluphenazine, haloperidol, molindone, and thioridazine in schizophrenics, as well as after single doses of chlorpromazine in normals. These alterations in REM after higher dosages seem to be lesser in degree.

(3) Tricylic antidepressants (amitriptyline and imipramine) appear to increase deep sleep stages and decrease REM activity.

(4) Hallucinogenic compounds decrease deep sleep stages, increase awake stages, and tend to attenuate REM activity.

The relatively consistent findings after anxiolytics, in contrast to the variable results of the studies with major tranquilizers, may be the result of the differences in populations (volunteers versus schizophrenics). The surprising finding is, however, the increase of REM characteristics (REM burst, REM single, and length of REM periods) after neuroleptics. Since, generally, the majority of CNS-effective drugs decrease REM activity, it will be important to investigate whether these results relate to the type of the population studied or to some other factors, such as the 'antipsychotic' effectiveness of the drugs, the extrapyramidal properties of these compounds, or perhaps the therapeutic response of the patients.

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