Eur Arch Psychiatr Neurol Sci (1986) 235:329–338

European Archives of Psychiatry and Neurological Sciences

Amitriptyline and Oxaprotiline in the Treatment of Hospitalized Depressive Patients

Clinical Aspects, Psychophysiology, and Drug Plasma Levels

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Summary. Amitriptyline (AT) and the noradrenaline reuptake inhibiting antidepressant oxaprotiline (OT = hydroxymaprotiline) were compared in 59 primary depressive inpatients in a 4-week double blind parallel group design. In the Hamilton Depression Rating Scale and 2 self-rating scales AT proved to be more efficient than OT, mainly with respect to disturbances of appetite and sleep. Agitated patients receiving OT needed more additional tranquilizing medication. The number of side-effects did not differ. Both drugs increased heart rate and skin resistance level (SRL) to about the same degree and did not influence the number of spontaneous fluctuations of SRL, habituation of SRL orienting responses (OR), frequencies of respiration and blinking. Salivation was temporarily more impaired by AT. All physiological variables differed between patients and 30 healthy controls during the whole 4-week trial. Clinical outcome showed a linear relation to OT plasma levels. For AT a therapeutic window was confirmed for concentrations of AT and its metabolite nortriptyline between 125 and 200 ng/ml. Patients whose SRL-OR habituated rapidly had a better outcome than slow habituators. Urinary excretion of 3-methoxy-4-hydroxyphenylglycol was lower in patients than in controls but could not predict outcome with either drug.

Key words: Primary depression – Amitriptyline – Oxaprotiline – Psychophysiology – Drug plasma level – MHPG

Introduction

Oxaprotiline (OT, hydroxymaprotiline), a tetracyclic antidepressant is a selective noradrenaline reuptake inhibitor with little anticholinergic and no 5 HT-blocking action (Delini-Stula et al. 1982a, b; Maitre et al. 1980; Waldmeier et al. 1977). Several open studies with inpatients (Bente and Fähndrich 1980; Schmauss et al. 1980) and outpatients (Feighner et al. 1981) demonstrated its antidepressant efficacy which was subsequently confirmed in controlled investigations: in one study it proved equal to maprotiline (Müller et al. 1983), in another less efficient than clomipramine (Wolfersdorf et al. 1983). Roffman et al. (1982) found OT to be superior to placebo and partly also to amitriptyline (AT). Here we report a further clinical double blind investigation of OT in comparison to a standard antidepressant. Amitriptyline was chosen as a reference mainly because of its influence on serotoninergic (Maitre et al. 1980) and cholinergic function (Szabadi et al. 1980) and its sedative properties (Kielholz 1973) which contrast to effects proven for or ascribed to OT.

The study was intended to answer the following questions:

(1) how do the antidepressant efficacies of AT and OT compare;
(2) is there a difference in both or either drug's effect on the syndromes of depressive agitation and retardation, or on endogenous (E) and nonendogenous (NE) depression?
(3) do drug plasma levels correlate with clinical effects?
(4) is there a connection between psychophysiological variables or urinary excretion of 3-methoxy-4-hydroxyphenylglycol (MHPG) before treatment and treatment response (response prediction)?
(5) do psychophysiological differences between patients and controls outlast the acute depressive syndrome (state or trait variables)?

Concerning points 3–5 we wanted to replicate and extend former findings of our group (Breyer-Pfaff et al. 1982; Gaertner et al. 1982a, b; Giedke et al. 1982). This article focuses on the psychopathological effects (points 1 and 2) and only briefly investigates the other topics.

Methods

Design

Fixed doses of OT and AT were given to primary depressive inpatients in a double blind, parallel group design study lasting 4 weeks. During a 1-week washout period 2 to 3 24-h samples of urine were collected for measurement of MHPG. One day before (D0) and on days 14 and 28 (D14, D28) of treatment psychopathological, psychophysiological, and laboratory data were sampled. Drug plasma levels were determined on days 14, 21, and 28. A group of healthy subjects was examined on days 0, 14 and 28 to control for self-rated mood, MHPG, and psychophysiological effects.

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Table 1. Experimental subjects

	Controls	All patients	RDC		ICD-9		Syndrome		Treatment	
			E	NE	E	NE	R	A	AT	OT
n	30	59	37	22	39	20	28	22	29	30
Age ($\bar{x} \pm SD$)	48 ± 10	47 ± 11	48 ± 12	45 ± 9	49 ± 11	42 ± 8	44 ± 12	51 ± 8	47 ± 12	47 ± 9
Males/females	8/22	18/41	10/27	8/14	13/26	5/15	10/18	5/17	7/22	11/19
RDC E/NE	–	37/22	–	–	29/10	8/12	22/ 6	11/11	18/11	19/11
ICD E/NE	–	39/20	29/ 8	10/12	–	–	22/ 6	12/10	23/ 6	16/14
Syndrome R/A	–	28/22 (9)	22/11 (4)	6/11 (5)	22/12 (5)	6/10 (4)	–	–	12/10 (7)	16/12 (2)
Tranquilizers on D14 and/or D28	–	23	16	7	16	7	8	13	9	14

RDC = Research Diagnostic Criteria
ICD = International Classification of Diseases
D14 = Day 14, D28 = Day 28 of treatment
E = Endogenously depressed
NE = Non-endogenously depressed
$\bar{x} \pm SD$ = mean ± standard deviation
R = Retarded depression
A = Agitated depression
AT = Amitriptyline
OT = Oxaprotiline

Subjects (Table 1)

All primary depressives in whom an antidepressive pharmacotherapy seemed necessary were asked to take part in the study. This approach was chosen in order to achieve as much as possible everyday practice. A total of 79 patients with a score of > 15 in the first 17 items of the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) entered the study, 59 completed it. All patients were between 18 and 66 years of age, free from severe somatic disease, and had given informed consent. With respect to their motor and verbal behavior 28 patients were classified as predominantly retarded and 22 as mainly agitated, in 9 classification was doubtful. As a deliberate restriction this classification was not operationalized but occurred as in clinical practice. According to the Research Diagnostic Criteria (Spitzer et al. 1978) 57 of the 59 patients suffered from a major depressive disorder (37 of endogenous subtype, RDC-E) and 2 from a minor depressive disorder; these 2 were included in the non-endogenous group of 22 patients (RDC-NE). At discharge, 39 of the 59 patients were diagnosed by the attending physicians as endogenously (ICD-E), 20 as non-endogenously (ICD-NE) depressed according to ICD 9.

Of the 20 drop-outs (3 men, 17 women) 5 were not due to medication: 3 patients remitted spontaneously (1 during washout, 2 on the first day of the investigation), 1 patient was not able to perform the psychophysiological tests, 1 woman's data were not considered because of continued atropine medication for surgical reasons.

From the remaining 15 (2 men, 13 women) 9 had been treated with AT (5 became psychotic, 1 dropped out for dry mouth and dizziness, 1 for dizziness, 1 for tiredness – she continued successfully with one-half the dose, 1 unexpectedly committed suicide in the 4th week) and 6 with OT (1 was noncompliant, 1 refused medication, 2 were dropped for insufficient response in the 2nd and 3rd week, 1 became restless and needed neuroleptics, 1 with an anorectic syndrome started to vomit severely in the 3rd week).

Some 30 healthy subjects with no history of psychiatric illness served as controls for self-rated mood, MHPG (D0 only), and psychophysiological variables during the course of the investigation. Mean age, and male/female distribution of the whole group of patients and controls were about the same (Table 1).

Treatment

Treatment started with 50–75 mg/day. From the 3rd or 4th day onward all patients received constant daily doses of 150 mg AT or OT in identical capsules of 25 mg divided in 3 portions of 50 mg at 8, 12, and 17 h.

It proved impossible to keep all patients free from additional medication. During the washout period, which was essentially a washout for antidepressants only, 16 of the 59 patients received benzodiazepine tranquilizers. Also 28 patients took tranquilizers at any time of the study (16 on D0, 16 on D14, and 22 on D28). Some patients were treated with cardiac glycosides and 1-thyroxine for medical reasons.

Procedures

Psychopathology. On D0, D14, and D28 each patient was (video-)interviewed in a semistructured way always by one of the same three experienced raters who marked the first 17 items of the HDRS. Immediately before the psychophysiological investigation 2 self-rating scales (v. Zerssen 1976) were filled in by the subjects, the Mood Scale (Befindlichkeits-Skala, Bf-S) which referred to the momentary mood and the Depression Scale (D-S) which referred to depressive symptoms of the past week. One patient was not able to complete the self-ratings on days 0 and 14 (resulting in 1 missing datum); on D0 15 further patients needed help from the technical assistant (self-ratings were always done in the morning, immediately before the psychophysiological investigation). On days 14 and 28 the attending physicians inquired about the side-effects of treatment.

Psychophysiology. A psychophysiological investigation was performed on days 0, 14, and 28. It comprised electroencephalographic variables (acoustically evoked potentials), contingent negative variation, postimperative negative variation; simple and associative reaction time, speech pause time; blood pressure, heart rate, finger pulse volume, respiration rate, blink frequency, salivation rate, surface electromyogram, skin resistance level (SRL) variables and habituation of the electrodermal orienting response (SRL-OR).

In the present context only blood pressure (Riva-Rocci), resting frequencies of heart beat (photoplethysmography of left middle finger), respiration (thermistor at nostrils), and blinking (measured by electrooculogram from upper and

Table 2. Psychopathological ratings (mean/standard deviation)

		Controls	All patients	RDC		ICD-9		Syndrome		Treatment	
				E	NE	E	NE	R	A	AT	OT
n		30	59	37	22	39	20	28	22	29	30
HDRS	D 0	–	23.6/ 4.8	25.2/ 4.6*	20.9/ 3.8	24.3/ 4.7	22.3/ 4.7	23.5/ 4.3	23.8/ 5.3	23.4/ 4.6	23.8/ 5.0
	D14	–	14.9/ 7.0	14.7/ 6.8	15.3/ 7.4	14.0/ 7.2	16.8/ 6.3	15.0/ 6.9	14.7/ 7.5	11.9/ 6.1	*17.8/ 6.5
	D28	–	10.4/ 6.9	9.9/ 6.9	11.2/ 7.0	9.4/ 7.2	12.3/ 6.1	11.8/ 7.9	8.6/ 5.8	8.6/ 6.5	(*12.1/ 6.9
Bf-S	D 0	9.5/6.9	43.0/ 9.8	44.9/10.1*	39.7/ 8.7	43.5/10.3	42.0/ 9.2	44.6/ 9.8	41.7/ 9.6	43.0/11.3	43.0/ 8.4
	D14	8.3/7.4	32.6/15.3	31.1/16.9	35.2/12.0	29.9/16.4	*38.3/11.4	33.0/15.8	30.5/16.8	29.8/14.4	35.3/16.0
	D28	7.7/7.3	28.0/17.0	26.6/17.7	30.4/15.8	24.2/17.1	*35.5/14.2	30.0/16.5	26.0/17.4	23.6/16.7	*32.3/16.3
D-S	D 0	5.1/3.2	28.7/ 9.3	28.8/ 8.2	28.5/11.0	28.1/ 9.2	29.8/ 9.4	28.9/ 8.2	29.5/ 9.5	26.1/10.1	*31.1/ 7.8
	D14	4.1/3.5	19.8/10.8	18.4/10.8	22.4/10.4	17.3/10.5	*24.9/ 9.7	18.9/10.4	19.9/11.8	17.2/ 9.1	(*22.3/11.7
	D28	3.7/3.0	16.3/10.9	15.1/10.3	18.3/11.8	13.2/10.3	*22.4/ 9.4	16.5/11.2	15.9/10.4	11.7/ 7.8	*20.7/11.7

D0, D14, D28 = Days 0 (before start), 14, and 28 of treatment HDRS = Hamilton Depression Rating Scale
Bf-S = Befindlichkeitsskala (v. Zerssen mood self-rating scale) D-S = Depressionsskala (v. Zersssen depression self-rating scale)
* = 2 $P < 0.05$; (* = 2 $P < 0.1$ (t-test for difference between neighboring groups); other abbreviations see Table 1

lower margin of the left orbit; gain 300 μV/cm; each deflection > 0.5 cm with an angle < 45° was considered a blink), SRL (10 μA constant current, electrodes on the palm of the left hand), habituation of SRL-OR to a series of 10 randomly spaced nonsignal tones (80 dB SPL, 1000 Hz, 0.5 s, interstimulus interval = 19 ± 4 s) – the number of tones to 3 successive failures to respond within 0.5–5 s after tone onset was taken as the measure of habituation, and salivation rate (3 dental swabs were placed sublingually and in each buccal sulcus for 2 min) are reported.

3-Methoxy-4-hydroxyphenylglycol (MHPG). MHPG was measured by gas chromatography after derivatization with pentafluoropropionic acid, using 4-methoxy-3-hydroxyphenylglycol as an internal standard. Coefficient of variation of repeated measures was 2% (Gaertner et al. 1980). The mean of 2 or 3 24-h samples, collected before D0, was used. All determinations were carried out in duplicate with a good correlation between the two assessments: r (p) = 0.99 for both patients ($n = 173$) and controls ($n = 78$).

Drug Plasma Level (DPL). Measurements were carried out on heparinized plasma stored at −20°C. Amitriptyline and its metabolites were assayed either by thin-layer chromatography (Breyer and Villumsen 1976) or by HPLC on C18-derivatized silica gel (modified from Preskorn et al. 1980). Results obtained with the two methods coincided. Oxaprotiline concentrations were determined by HPLC (Breyer et al. 1984).

Statistics

Analyses of variance (ANOVA) and of covariance (ANCOVA) were performed by the Generalized Linear Model (GLM, version 82.3) procedure of the Statistical Analysis System (SAS; SAS Institute 1982).

Results

1 *Psychopathology (Table 2)*

Analyses of variance with the factors time (D0, D14, D28) and treatment (AT, OT) resulted in the expected main effects of time. For the group of all patients a significant decline from D0 to D14 was seen in all ratings, from D14 to D28 in HDRS and D-S ratings only.

1.1 Comparison of AT and OT

There was a distinct superiority of AT over OT treatment which was statistically significant in the ANOVA for HDRS (main effect of treatment, F1, 57 = 7.50) and D-S (8.61) but not for Bf-S (2.64). As there were differences in the D0 ratings of D-S, ANCOVA with D0 scores as covariates were computed which yielded the same results.

An interaction of time X treatment showed up for HDRS only (F2, 114 = 4.99) indicating a better response to AT mainly on D14. On D28 all ratings favored the AT group (Table 2). If a HDRS score of ≤ 7 on D28 was arbitrarily chosen as a criterion indicating marked clinical amelioration 14/29 AT patients and 8/30 OT patients improved ($\chi^2 = 2.94$, $2P < 0.1$). If this criterion was extended to amelioration rates (100 − (100 × HDRS D28/HDRS D0)) > 50% the numbers changed to 19/29 AT and 16/30 OT patients (N.S.).

OT patients remained somewhat longer in the clinic after D28 than AT patients (39 ± 27 vs 27 ± 24 days, $t = 1.88$, $2P < 0.1$).

The superiority of AT over OT was mainly based on its influence on HDRS items 4–6 (sleep disturbances) and 12 (gastrointestinal symptoms). It did not seem to be an artifact of additional tranquilizing medication since the number of patients receiving benzodiazepines during treatment on D14 and/or D28 (9 AT, 14 OT) was about equal (cf., however, section 1.2).

Side-effects. Subjectively experienced side-effects are listed in Table 3. Dry mouth ranged first in both treatment groups and occurred in an about equal proportion – although objective reduction in salivation from D0 to D14 amounted to 33% in AT patients and only to 16% in the OT group (cf. 2.2). Cardiac arrhythmia and constipation were noted only in the OT group. There were no statistically significant group differences in the frequency on any side-effect; nor did the groups differ in the number of patients not complaining at all.

Table 3. Number of patients experiencing side-effects

	Amitriptyline ($n = 29$)		Oxaprotiline ($n = 30$)	
	D14	D28	D14	D28
No side-effects	11	13	7	9
Dry mouth	13	12	16	14
Disturbance of accomodation	3	4	3	2
Tremor	3	3	2	1
Hyperhidrosis	1	3	5	3
Dizziness	2	2	4	2
Tiredness	2	—	1	2
Headache	1	1	1	1
Restlessness	1	1	2	2
Cardiac arrhythmia	—	—	4	4
Constipation	—	—	2	1
Feeling of heaviness	—	—	1	1

D14, D28 = days 14 and 28 of treatment

Laboratory Values. In 6 cases there were slight increases of SGPT (4 AT, 2 OT) in 1 case (AT) of SGOT. In 2 cases (1 AT, 1 OT) alkaline phosphatase surpassed the normal range (= 2.5th to 97.5th percentile). An increase in urea was seen in 1 AT-treated woman who already had a slight abnormality on D0. Blood glucose level became elevated in 1 AT-treated patient. There was only 1 case of leukopenia (5300, 3700, 3500/mm^3 on days 0, 14, 28) in an AT patient. All deviations were small in amount, none caused cessation of therapy.

1.2 Agitated and Retarded Patients

Agitated patients experienced the same course during treatment as patients with depressive retardation. In 2-way ANOVAs (for HDRS, Bf-S, D-S) the main effects of syndrome and interactions of syndrome X time were not significant, even if D0 scores and age were taken as covariates. A 3-way ANOVA with time, treatment (AT, OT), and syndrome yielded no interactional effects which led to the conclusion that AT and OT are about equally suited to treat depressive agitation and retardation. This inference, however, needs qualification. As Fig. 1 shows, there was a marked difference in the psychopathological ratings of agitated patients treated with AT and OT. On D14 and D28 HDRS scores of these groups differed to a statistically and clinically significant degree (D14: $t = 3.50$, $2P < 0.01$; D28: $t = 2.20$, $2P < 0.05$). The same was so for D-S scores on D28 ($t = 2.25$, $2P < 0.05$). This shows that, notwithstanding the results of ANOVA, patients with agitation responded better to AT than to OT. The difference observed would have been even greater if additional tranquilizing medication had been equally distributed. During treatment, i.e. on D14, and/or D28, 13 of the 22 agitated patients and only 8 of the 28 retarded patients were taking benzodiazepines ($\chi^2 = 4.71$, $2P < 0.05$). Apparently, agitated patients stood in greater need of additional tranquilization. In particular, this was the case in OT treated agitated patients: of the 12 agitated patients who received OT, 10 were given tranquilizers on D14 and/or D28, of the 10 agitated patients receiving AT only 3 ($\chi^2 = 6.42$, $2P < 0.05$). In the retarded subgroup there was no such relationship.

1.3 RDC: Endogenous (RDC-E) Versus Non-endogenous (RDC-NE) Patients

On D0 RDC-E patients were rated more severely ill (HDRS, Bf-S) than NE patients (Table 2). The main effects of diagnosis on psychopathological ratings cannot be seen in ANOVA or in ANCOVA (when D0 ratings were entered as covariates). ANOVA indicated a significant interaction of

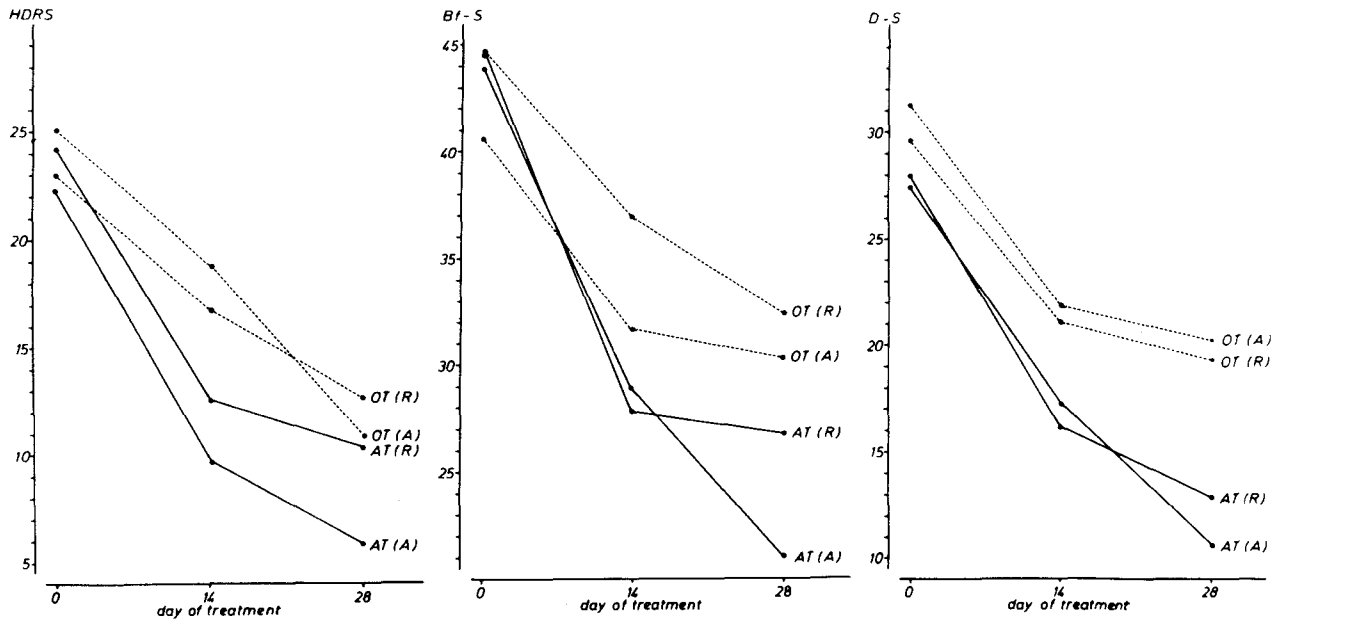

Fig. 1. Psychopathological ratings in retarded *(R)* and agitated *(A)* depressives treated with amitriptyline *(—— AT)* or oxaprotiline *(--- OT)*. HDRS = Hamilton Depression Rating Scale, Bf-S = Befindlichkeits-Skala (v. Zerssen mood self-rating scale), D-S = Depressions-Skala (v. Zerssen depression self-rating scale)

time × diagnosis (F2, 114 = 5.94, 3.27 in HDRS and Bf-S), which is an expression of the faster and more marked improvement of RDC-E patients. The percentage of patients who reached HDRS scores of ≤7, or amelioration scores of ≥50% on D28 did not differ between RDC-E and RDC-NE groups (38% vs 36%). After completion of the study RDC-E patients remained an average of 37 ± 24 days in the clinic, which is not statistically different from 27 ± 24 days for RDC-NE patients. Benzodiazepines on D14 and/or D28 were taken by 16/37 RDC-E patients and 7/22 RDC-NE patients (N.S.). There was no indication of a differential responsiveness of E or NE patients to AT or OT treatment (interactions of RDC diagnosis × treatment and diagnosis × treatment × time all N.S.).

1.4 ICD: Endogenous (ICD-E) Versus Non-endogenous (ICD-NE) Patients

At discharge each patient was diagnosed according to ICD9 by the attending physician who took into account all available information and was of course not blind to treatment outcome.

In a 2-way ANOVA (time and diagnosis) a significant main effect of diagnosis was apparent in the D-S scores ($F1,57 = 6.88$, E < NE), even if age was taken as a covariate ($F1,56 = 5.04$). As ICD-E and ICD-NE patients did not differ in D-S scores or in the other 2 ratings on D0, this is an effect of the poorer therapeutic outcome of ICD-NE patients which was also reflected in significant interactions of time × diagnosis in all 3 ratings ($F2,114 = 4.47, 5.48, 4.77$ for HDRS, Bf-S, and D-S). The difference between ICD-E and ICD-NE patients was especially marked in the self-ratings, both on D14 and D28 but did not reach significance for HDRS scores. However, significantly more ICD-E than ICD-NE patients reached a HDRS D28 criterion of ≤7 (46% vs 20%, $\chi^2 = 3.87$, $2P < 0.05$). Concomitant use of tranquilizers did not vary between these 2 groups. ICD-E patients were discharged somewhat earlier than ICD-NE patients (29 ± 22 vs 40 ± 32 days, N.S.). There is no indication that ICD-E or ICD-NE patients were more favorably treated with AT or OT (interaction of ICD diagnosis × treatment and diagnosis × treatment × time all N.S.).

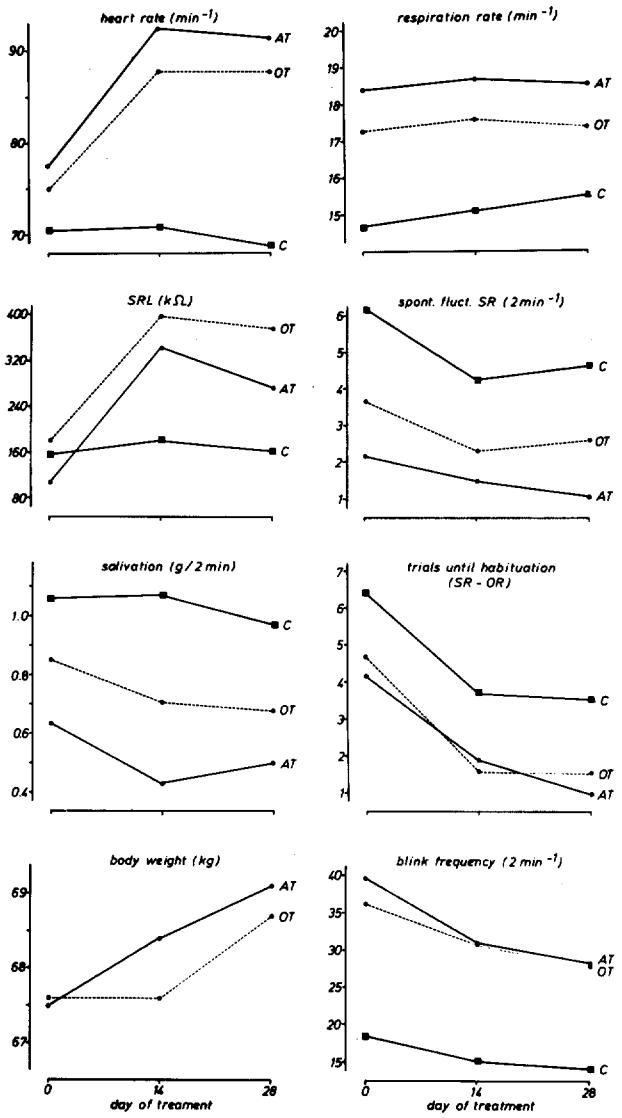

Fig. 2. (Psycho-)physiological variables in patients treated with amitriptyline *(AT)* or oxaprotiline *(OT)* and healthy controls *(C)* on days 0, 14, and 28 of the study

2 *(Psycho-)Physiology (Figs. 2, 3)*

2.1 Comparison of All Patients with Controls

Seven (psycho-)physiological variables were measured in both patients and controls: heart rate, respiration rate, salivation, blink frequency, SRL, spontaneous fluctuations of SRL, and habituation of SRL-OR. Group means of these variables can be seen in Fig. 2 (separate for patients treated with AT and OT). Two-way ANOVAs with time (D0, D14, D28) and group (patients, controls) yielded significant main effects of group in each variable and of time in all variables except respiration rate (salivation and fluctuations of SRL: effect of time only $P < 0.1$). In the case of SRL, effects of group and time were a result of medication: D0 values of SRL did not differ between groups; during treatment it increased in patients to about twice its initial level (skin became dry) whereas in controls it remained constant (interaction of time × group, $F2,171 = 3.97$, $P < 0.05$). In all other variables the group effects included D0 values: patients showed higher rates of heart beat, respiration, blinking, and habituation, they exhibited fewer fluctuations of SRL and had a lower salivation rate. At each of the experimental sessions and in each variable patient-control comparisons were statistically significant, $2P < 0.05$, *t*-test, with 2 exceptions, SRL on D0 (N.S.) and salivation rate on D0 ($2P < 0.1$).

During the 4-week investigation the heart rate of patients only became faster (interaction of time × group, $F2,172 = 25.31$, $P < 0.05$). This too is a clear effect of medication. Blink rate and number of fluctuations of SRL decreased, and habituation rate increased. These are pure effects of repetition as can be inferred from the near parallel course of changes in both groups and lacking in time × group interactions in ANOVA. Salivation rate remained about constant in controls but decreased by 1/5 in patients, which, however, did not show up in a time × group interaction. All changes observed, whether based on mere repetition or medication, were much more marked between D0 and D14 than between D14 and D28. None of the initial intergroup differences disappeared during treatment, some were even amplified.

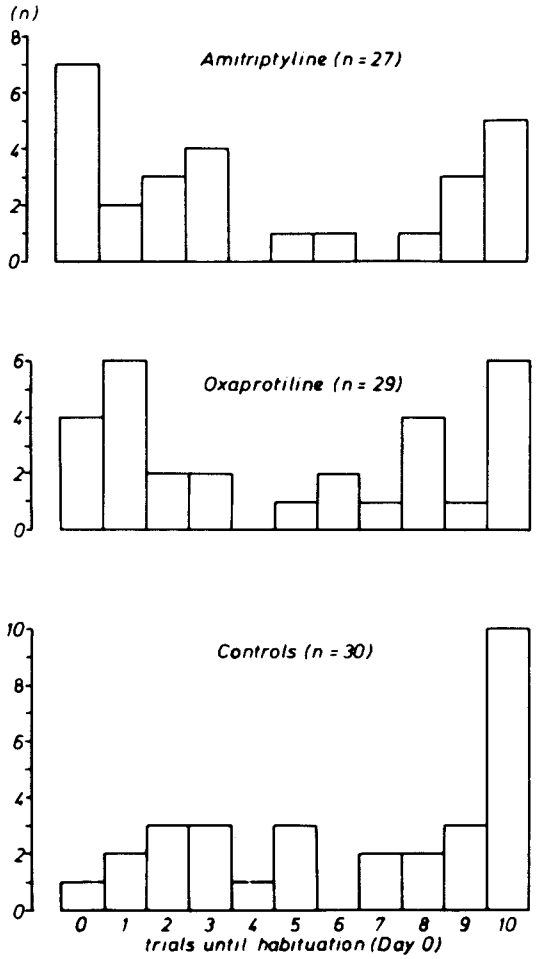

Fig. 3. Distribution of trials until habituation of the electrodermal orienting response on experimental day 0 in the 2 groups of patients later treated with amitriptyline or oxaprotiline and in healthy controls

2.2 Effects of AT and OT on Physiological Variables (Fig. 2)

In ANCOVAs with D0 values as covariates, main effects of treatment (AT, OT) were all insignificant. This was also true for salivation rate, although on D14 AT suppressed salivation more than OT (by 33% vs 16%). On D28 the difference had disappeared: 20% and 22% with respect to initial level.

From the 4 blood pressure (BP) variables (not shown in Fig. 2) systolic BP in the standing position reached significantly lower values on D14 in the OT than in the AT group (116 vs 125 mm Hg, $2P < 0.05$, t-test). All other BP variables, as well as heart rate in standing and sitting positions were essentially equal in the 2 groups.

There was only one interaction of treatment × time: body weight increased in both treatment groups but earlier and to a slightly higher degree in AT patients (F2, 113 = 4.79, $P < 0.05$). With this single exception AT and OT influence (psycho-)physiological variables to an astonishingly similar degree.

2.3 Physiological Variables in Retarded and Agitated and in E and NE Patients

Agitated patients were significantly older than retarded patients as were ICD-E vs ICD-NE patients. If this asymmetry in age is taken into account (ANCOVA) there was only one significant difference between groups. Systolic blood pressure (in sitting as well as in standing position) was higher in retarded as opposed to agitated patients (retarded: 127, 127, agitated: 123, 120 mm Hg main effect of group, F1, 47 = 9.87, 5.32) and in ICD-E as opposed to ICD-NE patients (E: 130, 128, NE: 117, 115 mm Hg, main effect of group F1, 56 = 9.49, 7.65). RDC-E patients did not differ from RDC-NE patients in any variable. There were no significant interactions between diagnosis or syndrome on the one hand and time on the other.

3 *Drug Plasma Levels*

The DPL of OT, AT and its principal metabolite nortriptyline (NT), which exhibits an antidepressant effect by itself are listed in Table 4.

In a former study (Breyer-Pfaff et al. 1982) with AT, in which a constant daily dosage of 150 mg was used, a therapeutic window for the concentrations of AT and NT was found: patients whose AT + NT levels (mean of days 14, 21, 28) ranged between 125 and 200 ng/ml had a significantly better clinical outcome than those outside this range. This relationship was confirmed in the present study and holds for both criteria, HDRS score D28 and HDRS amelioration score ($P < 0.025$ and 0.05, U-test).

Concerning OT, our hypothesis that clinical outcome is correlated to DPL can be accepted for amelioration scores ($r(s) = 0.36$, $P < 0.05$) but not for HDRS scores D28 ($r(s) = -0.28$, N.S.). The 7 patients who scored ≤7 in HDRS D28 displayed higher OT levels than the rest of the group (44 ± 20 vs 31 ± 11 ng/ml, $P < 0.05$, t-test). The OT levels of > 35 ng/ml were connected with lower HDRS scores on D28 ($P < 0.05$, U-test) and higher amelioration scores ($P < 0.025$, U-test).

4 *Relation Between Drug Plasma Level, Habituation Rate, and Clinical Outcome*

Fast habituation of the electrodermal OR has been found to be a predictor of favorable clinical outcome in schizophrenia (Frith et al. 1979; Zahn et al. 1981). In a previous study we could not confirm this for depressives but had the impression that habituation behavior and DPL might interact (Breyer-Pfaff et al. 1982).

In the present investigation we dichotomized the group of all those patients whose habituation scores and DPL were available. Nonresponders and fast habituators (0–3 reactions, $n = 32$) in the habituation experiment were compared to slow habituators and nonhabituators (5–10 reactions, $n = 26$). The cut-off point of 4 trials until habituation was chosen with re-

Table 4. Drug plasma level (ng/ml, mean ± SD)

	D14	D21	D28	$\bar{x}$ (D14, D21, D28)
OT	34 ± 15	34 ± 14	34 ± 16	34 ± 14
AT	85 ± 31	83 ± 34	78 ± 36	—
NT	73 ± 30	78 ± 43	70 ± 34	—
AT + NT	158 ± 48	161 ± 61	148 ± 60	154 ± 52

D14, D21, D28 = Days 14, 21, and 28 of treatment
AT = Amitriptyline, NT = Nortriptyline, OT = Oxaprotiline

Table 5. Clinical outcome as measured by HDRS with respect to DPL and habituation score before treatment (DO). Other abbreviations see Table 4

	Group	n	HDRS D28		
			$\bar{x} \pm SD$	t	$2P<$
1	Habituation score D0 0–3	32	8.4 ± 5.8	2.70	0.01
	Habituation score D0 5–10	26	13.1 ± 7.3		
2	DPL within therapeutic range	28	8.4 ± 6.6	2.63	0.02
	DPL outside therapeutic range	28	13.0 ± 6.6		
3	Habituation score D0 0–3 *and* DPL within therapeutic range	17	8.3 ± 6.3	3.83	0.001
	Habituation score D0 5–10 *and* DPL outside therapeutic range	15	16.3 ± 5.5		
4	AT + NT 125–200 ng/ml *and* habituation score D0 0–3	9	5.3 ± 6.2	2.95	0.02
	AT + NT outside 125–200 ng/ml *and* habituation score D0 5–10	7	13.7 ± 4.8		
5	OT > 28 ng/ml *and* habituation score D0 0–3	8	11.6 ± 4.7	2.79	0.02
	OT < 28 ng/ml *and* habituation score D0 5–10	8	18.6 ± 5.3		

spect to the distribution of habituation scores which shows a point of rarity at 4 (Fig. 3).

With respect to DPL one group was composed of patients whose AT + NT levels were inside the therapeutic window ($n = 13$) or beyond the median of OT concentrations (> 28 ng/ml, $n = 15$), the other by those outside the window ($n = 14$) or below the OT median ($n = 14$).

The result of this simple procedure shows that the habituation scores attained by the subjects on D0 (line 1 of Table 5) were about as closely related to therapeutic outcome as DPLs (line 2). The combination of both measures (line 3) was additive and separated treatment responders and nonresponders much more markedly. AT- and OT-treated patients contributed to this result to about the same degree (lines 4 and 5). When amelioration scores were used instead of HDRS scores the differences were the same. The number of fluctuations of SRL did not show a similar relation to therapeutic outcome.

5 *3-Methoxy-4-hydroxyphenylglycol*

There was a clear deficit in MHPG excretion in all patients ($n = 54$) as compared to normal controls ($n = 26$; 1830 ± 600 vs 2260 ± 520 µg/24 h, $2P < 0.05$, t-test). Subgroups of patients (E-NE, agitated-retarded) did not differ from each other. Responders (HDRS D28 < 7, $n = 6$) to OT treatment had an urinary output of MHPG of 1590 ± 620 µg/24 h, OT nonresponders (HDRS D28 > 14, $n = 11$) of 2000 ± 650 µg/24 h. This was a difference in the expected direction but not statistically significant ($t = 1.28$, $P > 0.1$, 1-tailed). For AT responders/nonresponders an inverse tendency was not observed.

Discussion

In this double blind parallel group study AT proved superior to OT in the treatment of major depressive inpatients. This showed up in the HDRS and two self-rating scales (Bf-S and D-S of von Zerssen). The advantage of AT is mainly based on its beneficial influence on disturbances of appetite and sleep. Its favorable sedative properties are also reflected in the significantly lower need for additional tranquilizing medication of those agitated patients who received AT as opposed to those receiving OT. This lends credit to the clinical practice of treating agitated patients with antidepressants of the "amitriptyline type" (Kielholz 1973). On the other hand, OT proved not to be superior to AT in the case of retarded depressives.

The concomitant use of benzodiazepines is a shortcoming of our study as these compounds have an influence on depressive symptoms (Schatzberg and Cole 1976) – especially when combined with antidepressants (Covi et al. 1981; Feighner et al. 1979; Johnstone et al. 1980; Rickels 1981). Fortunately, these drugs were about equally distributed; the slight preponderance of OT patients receiving tranquilizers may have decreased rather than increased the observed differences in efficacy. If we had insisted on strict monotherapy our study would have lasted much longer than the 4 years it took.

This general result is comparable to that of Wolfersdorf et al. (1983) who found clomipramine, another classic antidepressant, superior to OT in three of four self-rating scales and in global rating of physicians, but not in the HDRS scores of their inpatients. Roffman et al. (1982), however, who tested OT, AT, and placebo in a large multicenter sample of 278 outpatients, saw a superiority of OT over AT at the end of the treatment (i.e., after about 4 weeks) when treatment success was defined as a reduction in HDRS scores of > 50% and/or a HDRS final score of < 12 (which probably refers to the 21-item version of the scale). HDRS scores proper and Clinical Global Impression (CGI) scores did not show a difference and self-rating scores (Hopkins Symptom Check List) were not reported for unknown reasons. OT proved especially efficient in reduction of anxiety-somatization, AT however, as in our study, in sleep disturbances. A third study, in which OT was compared with its mother substance maprotiline showed no differences between treatments (Müller et al. 1983: 99 patients, 4 weeks, 150 mg, no self-rating reported).

Although the general result of the four controlled studies is not conclusive, it seems that OT has no convincing advantages over the antidepressants it was compared to. This is also reflected in the number of drop-outs and subjectively experienced side-effects in which we did not see distinct differences between AT and OT, either. Wolfersdorf et al. (1983) did not report on side-effects in their presentation, Müller et al. (1983) saw fewer side-effects in response to OT (as compared to clomipramine) as did Roffman et al. (1982) (in comparison to AT). It seems worth noting that all 5 psychotic decompensations in our trial happened in the AT group and all 4 patients who complained of occasional cardiac arrythmias (on

D14 and D28) were treated with OT. Feighner et al. (1981) observed one patient with "diffuse S-T-wave changes" at the start of OT treatment; Schmauss et al. (1980) found ECGs essentially normal in their 10 patients. Dry mouth was the main side-effect of OT in all studies which specified side-effects at all (Feighner et al. 1981; Roffman et al. 1982, 1983; Schmidlin et al. 1982). In contrast to Roffman et al. (1982, 1983) whose OT-treated patients complained significantly less of dry mouth than AT patients, our groups were essentially equal in this respect. But like these authors and also Schmidlin et al. (1982, healthy subjects, OT vs AT), we found a slight difference in favor of OT in the objectively measured salivation rate on D14 of treatment, which, however, disappeared on D28. The smaller sample makes our result less reliable than that of the "Oxaprotiline Study Group" (Roffman et al. 1982, 1983).

As with unwanted subjective side-effects, changes in laboratory data and (psycho-)physiological measures were not less frequent or less severe in OT than in AT-treated patients. Marked elevations in SRL by about 100% and in heart rate by 18% were seen in response to both drugs. As OT is reported to exhibit no (Delini-Stula et al. 1982b) or only very little anticholinergic activity (cf. Schmidlin et al. 1982) it is to be assumed that its antihistamine or noradrenaline potentiating effects cause the physiologic changes observed. The latter has been discussed by Schmidlin et al. (1982) with respect to the increase in heart rate. Actually, AT reduced heart rate in their healthy volunteers and had no influence on this variable in another study on healthy subjects (Szabadi et al. 1980). This is an obvious discrepancy to our results. In the present as well as in a previous investigation (Breyer-Pfaff et al. 1982) AT raised heart rate to a considerable degree. Apparently, the difference is due to the duration of treatment (single dose or 1 day treatment vs chronic treatment) or to the (healthy vs ill) subjects receiving it.

Whether salivation can be impaired by central or peripheral noradrenergic influence is unclear. There is a noradrenergic innervation of salivary glands which, however, promotes salivation and does not block it (Schramm and Selinger 1973). On the other hand, it is a common experience that stress and anxiety which increase the level of peripheral catecholamines (Frankenhaeuser 1975) are accompanied by dry mouth. A plausible interpretation seems to be that of Sigg (1968) who found that "central parasympathetic outflow is modulated by adrenergic mechanisms" and postulated that "adrenergic stimulation reduces parasympathetic activity, thereby resulting in a peripheral cholinolytic effect" (quoted after van der Kolk et al. 1978). In this way, the remarkable similarity in the spectrum of subjective and physiological side-effects of the two drugs including the increase in SRL could be explained. The noradrenergic effect is probably a central one as Schmidlin et al. (1982) did not see an increase in noradrenaline plasma levels after OT administration.

In contrast to the syndromes of agitation and retardation AT and OT did not differentially influence patients diagnosed as E or NE depressed, regardless of whether ICD or RDC diagnoses were used. There was, however, a distinctly better general outcome in E patients. This was more marked in the case of ICD diagnoses where it was partly an effect of E patients being older than NE patients (age and treatment outcome (HDRS D28) correlated significantly with each other, older patients did better ($r(s) = -0.43$, $2P < 0.01$); age as a covariate reduced the main effect of ICD diagnosis on psychopathological ratings). Also the fact that ICD diagnoses were discharge diagnoses may contribute. Probably there is a tendency to diagnose relatively young patients who do not improve as NE or neurotic. On the other hand, RDC diagnoses which were given at the start of the investigation point to a better outcome of E patients. They were rated more severely ill at the beginning (which is, among other things, an effect of the greater number of depressive symptoms RDC-E patients have to fulfill) and improved to a greater degree than NE patients, but were rated as markedly improved (HDRS D28 $\leq$ 7) to about the same percentage (38% vs 36%) at the end of the experiment.

In this connection it is worth noting that only 37% of our patients were rated markedly improved (HDRS D28 $\leq$ 7) after this 4-week study, thus matching the self-rating scores. On D28 39% (Bf-S) or 41% (D-S) of the patients scored lower than the respective mean plus 1 SD of a large normal sample (v. Zerssen 1976). If the ratings of our healthy controls were taken the result would be even poorer. This reflects the fact that increasingly more therapy resistant patients are admitted for inpatient treatment.

According to the noradrenaline hypothesis of depression, patients with low excretion of MHPG should respond particularly well to noradrenaline reuptake inhibiting drugs, whereas high MHPG excretors would do better with drugs like AT (also) influencing serotoninergic systems (Maas et al. 1972; Schildkraut 1974). Actually, a corresponding tendency was shown for maprotiline (Gaertner et al. 1982a) which is a strong noradrenaline potentiating compound (Maitre et al. 1980) and also for AT (Gaertner et al. 1982b). In the present study both results were not confirmed. AT responders and AT nonresponders did not differ in initial MHPG excretion. MHPG in responders to OT, which inhibits noradrenaline reuptake comparably to maprotiline (Maitre et al. 1980) differed from that of OT nonresponders indeed, but not significantly so (1585 vs 2000 µg/24 h, $t = 1.28$, $P > 0.1$). Roffman and Gould (1982) observed that patients with a low basal excretion of MHPG responded even less favorably to OT than to AT. Thus, the empirical basis for therapeutic recommendations based on MHPG excretion alone seems insufficient.

Allowance should be made for a number of methodological handicaps in the collection of MHPG data which may have affected our results adversely. There is no agreement concerning the influence on MHPG excretion of both intake and withdrawal of neuroleptics and antidepressants (in this respect our washout period of 1 week may have been too short), of food composition and of gross motor activity (these were not controlled in this study). Accuracy and completeness of urine sampling was stressed but often cannot be sufficiently supervised in psychiatric patients.

A recent report on the use of DPL determinations in psychiatry (Task Force 1985) notes either linear or curvilinear relations between different antidepressants and their clinical effect. The drugs used in the present study may serve as examples for these two categories. In the case of OT – which to our knowledge has not been investigated in this respect – there was (as, e.g., with imipramine) a slight, significant positive correlation between mean DPL and percent amelioration in HDRS. That suggests that in our study the therapeutic results with OT possibly would have been better with a higher daily dosage.

Concerning AT we confirmed our earlier finding (Breyer-Pfaff et al. 1982) of an optimal therapeutic range for concentrations of AT and its principal metabolite NT between

(AT + NT) = 125–200 ng/ml. DPLs outside this therapeutic window are linked to a significantly poorer outcome than those inside. This replication of our finding, which agrees with those of Montgomery et al. (1979), Moyes et al. (1980) and Vandel et al. (1979), is a strong argument for a therapeutic window for AT + NT in this otherwise "unresolved issue" (Task Force 1985).

As steady state DPLs can be inferred from single dose kinetics with a high degree of certainty (Brunswick et al. 1979; Madakasira et al. 1984; Redmond et al. 1980) regular relationships to clinical outcome as those reported here for AT may help find the right dose for an individual patient early in therapy and predict therapeutic outcome.

As our results show, prediction may be improved if, in addition to DPL, habituation rate is also taken into account. This variable discriminates depressive and schizophrenic (Giedke et al. 1982) and possibly other disease groups from healthy controls. As can be seen from our present findings as well as from those of Iacono et al. (1983, 1984) who investigated depressed patients in the free interval, fast habituation seems to be a trait rather than a state dependent variable. We consider it one sign of a favorable spontaneous prognosis independent of therapeutic influences, in contrast to DPL which primarily refers to therapy specific aspects. The relation between habituation score and clinical outcome seems not to be as robust as that between DPL and therapeutic success because we could not observe it in our former study with AT (Breyer-Pfaff et al. 1982). However, similar observations in schizophrenic patients (Frith et al. 1979; Zahn et al. 1981) suggest that we are facing a general, nosologically unspecific principle of a certain protective value which has been repeatedly pointed out by Heimann (1977, 1979).

More details about the psychophysiological aspects of this study will be reported separately. We merely want to briefly underline the physiological differences our depressive patients showed in comparison to healthy controls: the depressive organism seems to be the more active (higher rates of heart beat, respiration, blinking). Also dry mouth can be interpreted as a sign of heightened arousal (cf. Giedke 1983). Taking this into account, the suggestion seems plausible that fast habituation and small numbers of spontaneous fluctuations of SRL are not simple deficits but a sign of active inhibition (Heimann et al. 1977).

Acknowledgement. The study was supported by the Deutsche Forschungsgemeinschaft (DFG, Gi124/1,2). We are indebted to Helga Pimpl for her continued manifold help and to Agnes Mahal and Beate Wolf for technical assistance.

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Received July 24, 1985