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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 01-009904- 00009-0000
Fec: 2008-11-02 17:23:15 Dep. 2020 NUECREACIONES
Tra. 2 PATENTES
Eve: 1 REGDEPOSITO
Act 444 RESPUESTAREQUE Folios: 30

Trámite: 002

Evento: 001

Actuación: 444

Referencia : Expediente No. 01009904

Asunto : Solicitud de patente para: **UNIDAD DE DOSIS DE MIRTAZAPINA
PARA EL TRATAMIENTO DE TRASTORNOS DEL SUEÑO**

Solicitante : AKZO NOBEL N.V.

Fecha de Solicitud : 9 de febrero de 2001

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al oficio número 8373 notificado por fijación en lista el 3 de agosto de 2006.

2. Mediante el oficio número 8373 se puso en conocimiento del solicitante el Informe que contiene las observaciones hechas por su Despacho sobre el examen de fondo de la presente solicitud de patente.

3. Atiendo a las observaciones realizadas mediante el oficio número 8373 de la manera siguiente:

Presento junto con este memorial copia de los artículos requeridos por su Despacho con el fin de realizar un análisis de la patentabilidad de la presente invención.

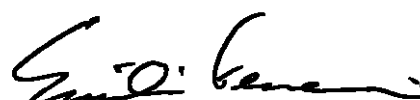
4. DOCUMENTOS ADJUNTOS: Junto con este memorial presento los siguientes documentos:

1) DATABASE DRUGNL "Organon's Mirtazapine Still available for licensing in the USA"
Database accession No. 92:603, XP002164421 & R&D FOCUS DRUG NEWS

2) E. VESTER ET AL.: Anxiolytic and sleep improving effects of mirtazapine in everyday clinical practice" EUROPEAN NEUROPSYCHOPHARMACOLOGY, Vol 7, no. SUPPL. 2, 1997, page S175 XP000981394.

- 3) RAMAEKERS J G ET AL: " Effects of nocturnal doses of mirtazapine and mianserin on sleep and on daytime psychomotor and driving performance in young, healthy volunteers". HUMAN PSYCHOPHARMACOLOGY, Vol. 13, no, SUPPL. 2, November 1998. pages S87-S97, XP000979860. /
- 4) RUIG G S ET AL: "Effect of the antidepressant ORG-3770 on human sleep" EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, Vol 38, no. 6, 1990, pages 551-554, XP 000979975. /
- 5) WESTENBERG HERMAN G.M: "Pharmacology of antidepressants: Selectivity or multiplicity?" JOURNAL OF CLINICAL PSYCHIATRY. Vol. 60, no.SUPPL. 17, 1999, pages 4-8, XP000979957. /
- 6) SITSEN J M A ET AL: "Mirtazapine a novel antidepressant in the treatment of anxiety symptoms: Results from a placebo-controlled trial" DRUG INVESTIGATION, Vol. 8, no. 6, 1994, pages 339-344, XP000981393. /

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COLO 11214-801-024-5
JDF/JDF/
ID-000607/WPC11214
Cns M-2006-00012568

92:603 DRUGNL

XP-002164421

Organon's Mirtazepine Still Available for Licensing in the USA
R&D Focus Drug News (13 Jul 1992).

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Organon's antidepressant drug, mirtazepine (ORG 3770, REMERON), is still available for licensing in the USA and Japan. Marketing approval is still awaited in Europe, the submission for this region was made in April 1991. Phase III trials have now been completed in the USA.

Mirtazepine is an α_2 -antagonist acting at the presynaptic receptors. It shows no monoamine uptake blocking activities. This compound is a potent antidepressant with anxiolytic and hypnotic properties with a good toxicity profile. It has few anticholinergic side-effects and little cardiovascular toxicity. For further information on the licensing opportunities with mirtazepine contact: Mr Schikan, Licensing Department, Akzo BV, POB 20, 5340 BH Oss, The Netherlands, Tel: (31) 4120 62945; Fax: (31) 4120 62522; Telex: 37503 AKPHA.

Licensing Contact: Mr Schikan, Licensing Department, Akzo BV, POB 20, 5340 BH Oss, The Netherlands, Tel: (31) 4120 62945; Fax: (31) 4120 62522; Telex: 37503 AKPHA

N mirtazepine; mepirzepine; azamianserin; ORG 3770; REMERON; ZISPIN
N 61337-67-5
N6A Psychoanaleptics, Antidepressants
Organon
STA licensing offer. United States; Japan

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XP-000981394

P.O. 1-9-1997
P. 5175**P.1.126** Anxiolytic and sleep improving effects of mirtazapine in everyday clinical practiceE. Vester, J.T.H. Helsdingen. *NV Organon, Oss, The Netherlands*

Aims: To assess anxiolytic and sleep improving effects of mirtazapine (15-60 mg/day) in depressed outpatients in an open-label, non-comparative, naturalistic study.

Materials and Methods: Patients in need of pharmacological treatment with antidepressants as assessed by psychiatrists or GPs in The Netherlands, were included in the study. Participating psychiatrists were working in different clinical settings, involving primary, outpatient and inpatient care. A specially developed check-list in Dutch language for global assessments of efficacy and safety by a physician were used in this study. The patients were assessed at screening, and 1, 2 to 3 weeks and 3 months after beginning the treatment with mirtazapine. The investigators had the option either to start with mirtazapine 15 mg/day for 4 days, and to increase to 30 mg/day from day 5, or to start with 30 mg/day from day 1 onwards. The maximum allowed dosage of mirtazapine was 60 mg/day. Two subgroups were identified among patients diagnosed with depression ($n = 539$): with high baseline anxiety ($n = 329$) and sleep disturbances ($n = 473$). Efficacy and tolerability of mirtazapine were assessed during a 3-month treatment period.

Results: Improvements in depressed mood, symptoms of anxiety and sleep disturbances, as assessed by check-list, were seen in similar percentages of anxious patients at each visit and at endpoint. In general, a global improvement at endpoint in either symptom was seen in approximately 65% of patients. The overall drop out rate in anxious patients was 21%, while the percentage of patients complaining of at least one adverse event progressively decreased during the study period, from 46% at visit 1 to 21% at visit 3. The only adverse events registered in more than 5% of patients were somnolence at all three visits (in 29%, 18% and 8% of patients, respectively), and dizziness in 9% and 5% of patients at first 2 visits. The patient population with high initial sleep disturbance responded favourable to treatment with mirtazapine. Improvements in mood, symptoms of anxiety and sleep disturbances were seen at endpoint in 66%, 45% and 70% of patients, respectively. The overall dropout rate was 20%. As in the subgroup of anxious patients, the percentage of patients complaining of at least one adverse event progressively decreased during the study period, from 46% at visit 1 to 21% at week 3. The only adverse events reported in more than 5% of patients were somnolence (in 28%, 19% and 9% of patients at 3 assessment times) and dizziness in 9% of patients at week 1. In conclusion, the results of this open-label study suggest that mirtazapine has favorable efficacy and is well tolerated in depressed outpatients presenting with high anxiety or sleep disturbances.

XP-000979860

P.D.	11-1998	11
P.	987-97	

HUMAN PSYCHOPHARMACOLOGY

Hum. Psychopharmacol. Clin. Exp. 13, S87-S97 (1998)

Effects of Nocturnal Doses of Mirtazapine and Mianserin on Sleep and on Daytime Psychomotor and Driving Performance in Young, Healthy Volunteers

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Eighteen healthy volunteers participated in a randomized, double blind, cross-over trial. They received mirtazapine, mianserin or placebo during separate periods of 15 days. Mirtazapine and mianserin were respectively administered doses of 15 mg and 30 mg nocte for the first 7 days and doses of 30 mg and 60 mg nocte for the remaining 8 days. Assessments were made at baseline and on days 2, 8, 9 and 16 of each period to compare effects of drugs and placebo on mood, psychomotor (CTT, CRT, CFF and Vigilance) and 'actual' driving performance. Sleep quality and duration and side-effects were assessed at baseline and every treatment day. Mirtazapine 15 mg and mianserin 30 mg slightly impaired psychomotor and driving performance on day 2 of treatment. On day 8, the effects were virtually gone, although some driving impairment could still be observed in the mianserin condition. No drug effects on performance were found on day 9 despite the dose escalation. On day 16 of treatment, driving performance and vigilance slightly decreased in, respectively, the mirtazapine and the mianserin conditions. These effects indicate that tolerance to the drugs' adverse effects was not complete. This observation was also supported by subjective data. Similar increments in sleep duration and findings of lethargy, drowsiness and weakness were observed throughout treatment with both drugs. Alertness and contentedness was always lower during both drug treatments than with placebo. Spontaneously reported adverse events were similar to self-rated side-effects and more of both were recorded during mianserin treatment. It is concluded that the acute and subchronic effects of nocturnal doses of both drugs were similar and equally low in magnitude. Effects on performance were much less than those seen in other studies after administration during the day. Full daily doses of both drugs should be prescribed in nocturnal dosing regimens, and not in divided doses over the day, for avoiding excessive sedation and performance impairment. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — mirtazapine; mianserin; sleep; driving performance; impairment; psychomotor function

INTRODUCTION

Mirtazapine is a new piperazinoazepine antidepressant. Its chemical structure is similar to mianserin but its mechanism of therapeutic action differs (De Boer and Ruigt, 1995; De Boer, 1996; Kelder *et al.*, 1997). Both drugs have strong binding affinities for presynaptic α_2 adrenergic auto- and heteroreceptors as well as postsynaptic

serotonergic 5-HT₁, 5-HT₂ and histaminergic H₁ receptors where they act as antagonists of the endogenous ligands. Neither has any affinity for muscarinic receptors and mirtazapine, in contrast to mianserin, has little for α_1 receptors. The blockade of α_1 autoreceptors on noradrenergic neurons enhances the synthesis and release of noradrenaline. The enhanced rate of noradrenaline release stimulates α_1 receptors on serotonergic neurons and subsequently enhances serotonergic cell firing. Further facilitation of 5-HT release is caused by mirtazapine's antagonistic activity at α_2 heteroreceptors located at axonal terminals of serotonin neurons. By specific blocking both post

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synaptic 5-HT₂ and 5-HT₁ receptors the net effect of mirtazapine within the serotonergic system is to indirectly enhance neurotransmission at 5-HT₁ receptors. The remaining site of antagonistic mirtazapine activity, the H₁ receptor, is not thought to mediate an antidepressant effect. Rather H₁ blockade causes sedation that may be desirable or unwanted depending upon the patient's condition and when the drug is taken during the circadian cycle. Mirtazapine is rapidly absorbed and reaches T_{max} within 2 h. The drug undergoes substantial 1st pass metabolism resulting in about 50% bioavailability (Voortman and Paasakker, 1995). The contribution of the active metabolite to the total pharmacodynamic profile of mirtazapine is relatively low, i.e. 3–6% (Delbressine and Vos, 1997). Elimination of the parent and its active metabolite occur with a half-life of 20–40 h. Steady state is reached within 3–5 days of continual, once daily dosing (Timmer *et al.*, 1995). The therapeutic dose range is 15–45 mg/d. Mirtazapine is generally given at night to promote sleep and avoid unwanted daytime sedation.

Phase I tolerability trials (Data on file) showed that single doses of 15, 30 and 45 mg main produced mild to moderate sedation that appeared to be dose-related in healthy volunteers. Postural hypotension and consequently dizziness were found after doses of 30 and 45 mg. Repeated ascending doses up to 60 mg caused subjective feelings of sedation at all levels, but postural hypotension dissipated with developing tolerance. The effects of single doses of mirtazapine on psychomotor performance and sleep were investigated in two studies. Mattila *et al.* (1989) administered morning doses of mirtazapine 15 mg, amitriptyline 50 mg and placebo alone and in combination with 15 mg diazepam to 12 young, healthy volunteers. Mirtazapine impaired performance in several tests of psychomotor performance (Tapping, CFF, Maddox wing, Postural Instability) and increased feelings of drowsiness and passiveness between 1, 5 and 6 h post drug. The investigators judged the degree of impairment after mirtazapine to be about equal to that of amitriptyline. Neither drug's effect was potentiated by diazepam. Rulgt *et al.* (1990) investigated the effects of a single dose of 30 mg nocte on sleep and psychomotor performance in a placebo controlled study involving six healthy volunteers. EEG recordings showed a reduction in nocturnal waking and an increase in deep, slow-wave sleep. Psychometric tests (Reaction time and Vigilance)

conducted the next morning at 16 h post drug showed no effect of mirtazapine. Subchronic effects of mirtazapine on psychometric performance were studied in a pilot study by Robbe *et al.* (1994). Six volunteers were treated with ascending evening doses of 15, 30 and 45 mg for 19 days. Two other volunteers received placebo in parallel. Moderate impairment was found between 12 and 17 h after the initial dose on almost every psychometric test (CFF, Tracking, Divided Attention and Vigilance). Subsequent doses did not affect performance, indicating that the development of tolerance occurred at a faster rate than the ascension of mirtazapine's plasma concentration. However, subjective feelings of drowsiness persisted throughout the treatment period.

These studies suggest that whatever impairing potential mirtazapine might have, it is mitigated in whole or part by nocturnal dosing and sleep. Because patients following the recommended dosing regimen will take the drug in this manner it seemed essential to determine what the drug's effects on performance are over the days following nocturnal dosing. This study was designed for that purpose. It compares the effects of ascending doses of mirtazapine, with equipotent doses of mianserin and placebo on psychomotor and actual driving performance in healthy volunteers. Mianserin was chosen as an active control because of its well known sedative potential (Seppälä, 1977; Curran and Lader, 1986; Mattila *et al.*, 1978), but also because it is in structure most related to mirtazapine. Effects on performance were expected to differ between drugs if their differential affinities for α_1 adrenoceptors is a determining factor.

METHODS AND MATERIALS

Subjects

Eighteen healthy volunteers, nine males and nine females, were recruited by newspaper advertisements. Initial screening was accomplished on the basis of replies to a medical history/driving-experience questionnaire. Qualified individuals were physically examined by the Medical Supervisor who also obtained blood samples and a standard 12-lead electrocardiogram from each one. Standard blood chemistry and hematology assays were conducted on those samples. Subjects were included if they satisfied the following criteria: possession of a valid driver's licence, aged 21–35 years, normal binocular visual acuity,

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corrected or uncorrected. Exclusion criteria were as follows: excessive smoking, positive urine drug screen at screening, history of psychotic illness, drug abuse, cardiovascular disease, unusual sensitivity to medicinal drugs, renal, hepatic or neurological disease. The study was carried out in accordance with the World Medical Association's declaration of Helsinki (Hong Kong Modification, 1989). It was approved by the standing Ethics Review Committee of Maastricht University. Written informed consent was obtained from each subject prior to participation.

Design and treatments

Treatments were administered in separate 15-day series, according to a placebo controlled, 3-way, double-blind, cross-over design. Treatment orders were originally balanced and assigned to subjects by exhaustive random selection from six independent 3×3 Latin Squares. Subjects received the following treatment regimens during respective treatment periods: mirtazapine 15–30 mg, mianserin 30–60 mg and placebo. Dosing started the evening before (day 1) the first test day (day 2). Subjects received 15 mg of mirtazapine and 30 mg of mianserin during the first seven days of treatment, and respectively 30 and 60 mg on subsequent days. Drugs and placebo were always ingested at fixed times in the evening. At baseline and on days 2, 8, 9 and 16 of each treatment series, subjects undertook a sequence of performance tests and subjective assessments of mood according to a fixed schedule, between 15 and 18 h following the evening dose.

Performance assessments

Training occurred in two sessions prior to application of treatments. Training in Critical Fusion Frequency (CFF), Critical Tracking (CTT) and Choice Reaction Time (CRT) continued until the subject had performed each one with less than 5% of the variance from the average measured over the final three trials. Performance on the sustained attention test (VIG) and the standard Highway Driving Test show little practice effects, so for these, training simply involved the administration of one trial.

CFF (Hz) is the visual system's threshold for repeatedly responding to and recovering from discontinuous (on-off) light stimulation. Trains of stimuli arriving at the retina at frequencies below

the CFF threshold are perceived as flicker, those above, as constant light (Vuurman *et al.*, 1991).

CTT measures the subject's ability to control a displayed error signal in a 1st-order compensatory tracking task. Error appears as horizontal deviation of a cursor from midpoint on a horizontal, linear scale. The subject is required to make compensatory joystick movements that null the error by returning the cursor to the midpoint. The frequency of cursor deviations, and therefore its velocity, increases as a stochastic, linear function of time. The subject is required to make compensatory movements with a progressively higher frequency. Eventually this response frequency lags the error signal by 180°. At that point the subject's response adds to, rather than subtracts from, the error and control is lost. The frequency at which the subject loses control is commonly defined as λ_c (the 'critical frequency'). The reciprocal of this frequency is theoretically the perceptual/motor delay for humans operating in closed-loop system. As such it is analogous to a 2-choice reaction time in discrete responding tasks. The subject performed this test in five trials on each occasion. The mean λ_c (rad/s) was recorded as the final score (Jex *et al.*, 1966).

CRT (ms) measures the subject's average reaction time to the words 'left' and 'right' using corresponding push-buttons. Half of each type are presented at compatible and incompatible (i.e. left and right) position on a computer display. Average reaction time was scored over 48 trials.

VIG has been extensively used in studies on human vigilance performance (Mackworth, 1950). Subjects are seated in front of a computer screen displaying a circular arrangement of 60 dots simulating the second marks on a clock. Dots are briefly illuminated in clockwise rotation at a rate of one per second. Usually the rotation proceeded with a 6° 'jump'. Subjects are instructed that at rare, irregular intervals the target proceeds with a 12° jump by skipping one of the dots in the normal sequence. This 'double jump' is the signal to which subjects respond by pressing a button. The dependent variable of the test is the number of correct detections; the test lasts 45 min.

The Highway Driving Test has been used for drug screening purposes in The Netherlands since 1981 (O'Hanlon *et al.*, 1982). It was standardized the following year and has been applied in essentially the same manner ever since. The subject's task is relatively simple. He/she enters a primary highway (4-lane, divided) at the beginning

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of a 100 km circuit. He/she then proceeds to drive while attempting to maintain the vehicle at a constant speed (95 km/h) and steady lateral position between the delineated boundaries of the slower traffic lane. The subject is allowed to deviate from this procedure in order to pass slower vehicles travelling in the same lane. At an intersection halfway through the circuit, the subject drove off the highway and re-entered travelling in the opposite direction.

The subject was accompanied by two investigators. A technician, whose task was to operate the equipment, was present in the rear passenger's seat. A licenced driving instructor was seated in the front passenger's seat with access to dual controls. His sole function was to ensure test safety. Subjects were instructed to operate safely at all times and that the treatments might affect their ability to do so. They were informed of their legal responsibility to stop a test in progress if feeling for any reason that to continue would be unsafe. They were further informed that they would be asked to stop by the instructor if, in his opinion, their physical appearance or driving performance indicated the possibility of a control loss. In the event that a subject chose to stop or was told to do so by the instructor, he/she was required to first signal and then bring the vehicle to a gradual halt on the paved shoulder of the road.

Several electronic signals indicating the driver-vehicle-road interaction were automatically recorded during the test. The most important was acquired by an electro-optical device which continuously measured the lateral distance separating the vehicle and the left lane-line. This signal was digitized at a rate of 4 Hz and stored on an on-board computer disk file for later editing and analysis. The off-line editing routine involved removal of all data segments that revealed signal loss, disturbance or the occurrence of passing manoeuvres. Clean data were then reduced within successive 5 km segments to yield corresponding means and variances for lateral position. The square root of the variance pooled over all segments, or total standard deviation of lateral position (SDLP), was then taken as the dependent variable for the Highway Driving Test.

Assessments of mood

A series of 16, 100 mm horizontal visual analog scales were used to subjectively evaluate changes in mood experienced by the subject as a result of the

treatment. Subjects were asked to indicate how they felt at the time of testing by drawing a vertical line on each scale; the ends of each scale represent the opposite extremes of a given state (drowsy-alert, tense-relaxed, etc.). The subject was told that each scale represents the entire spectrum of each mood state. The result was measured in mm from the right end of the scale. Using this test, three factors, i.e. alertness, contentedness and calmness can be calculated on the basis of a main component analysis (Bond and Lader, 1974).

CNS and sleep assessments

Side-effects were recorded by subjects on separate 100 mm visual analogue scales. The items included drowsiness, lack of concentration, memory disturbances, dizziness, nausea, weakness, headache, lack of coordination, dry mouth and lethargy. Sleep was assessed by subjects using the 'Groning' Sleep Questionnaire (Muller-Hajonides van der Meulen, 1981). This is a standard clinical sleep quality questionnaire describing the quality and duration of sleep. Sleep questionnaires were completed following waking on baseline and days 2-16 of treatment. Side-effects were assessed in the evening of the same days. For analytical purposes they were later averaged over three assessment days to construct five consecutive time periods that covered the whole treatment. Averages were made over days 2-4, 5-7, 8-10, 11-13 and 14-16.

Pharmacokinetics

Blood samples were collected on days 2, 8, 9 and 16 of treatment. Mean plasma concentrations were determined by capillary Gas Chromatography with Nitrogen-Phosphorous-selective Detection (GC-NPD). Extraction from alkalinized plasma was performed with *n*-hexane. The limit of quantification was 0.2 ng/ml.

Statistics

Analyses were carried out by means of the SPSS/PC + program series to investigate whether the effects of mirtazapine and mianserin on performance differed from those of placebo (H_0). Performance during treatment was adjusted for initial differences at baseline by means of a standard analysis of covariance. Adjusted scores of psychomotor and driving performance and mood were analyzed at every time point using a

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two factor ANOVA (Subjects and Treatment). Mean-contrast (drug versus placebo) tests were conducted for measuring the significance of contributions of each, individual drug to the overall Treatment effect. These specific drug-placebo comparisons were made independently of the corresponding overall effect. This is a legitimate procedure if the comparisons are built into the design or suggested by the theoretical basis for the experiment (Winer, 1962). The pooled within subject residual variance was used as the error term for conducting all tests within a particular set.

Adjusted means of sleep parameters and subjective side-effects were not normally distributed. They were analyzed by the non-parametric Friedman test to detect main differences between treatments and placebo. These were followed by Wilcoxon's signed-rank tests to compare the effects of treatments and placebo on separate treatment days.

RESULTS

Drop-outs

One subject withdrew from the second period after 10 days of mianserin treatment. Another subject stopped participation prior to his third period, in anticipation of a possible recurrence of side-effects he had experienced during the first period (mianserin), i.e. apathy and loss of libido. Consequently, both subjects did not participate in the third period wherein they would have been treated with mirtazapine. In total 16 subjects completed the study.

Psychomotor and driving performance

Summary of significant and nearly significant results from the statistical analyses are given in Table 1. Treatment effects on CTT and SDLP reached significance on day 2 and days 2 and 9 respectively. Drug-placebo comparisons revealed impairing effects on CTT of both drugs on day 2 of treatment. They also showed elevated SDLP values on day 2 and 16 of treatment with mirtazapine and on day 8 with mianserin, though the latter just failed to reach significance. Mean (SE) CTT and SDLP values in every treatment condition are shown in Figure 1. Mianserin also decreased the number of correct detections in the sustained attention test on day 2 of treatment. On day 16, the effect of mianserin on sustained attention approached

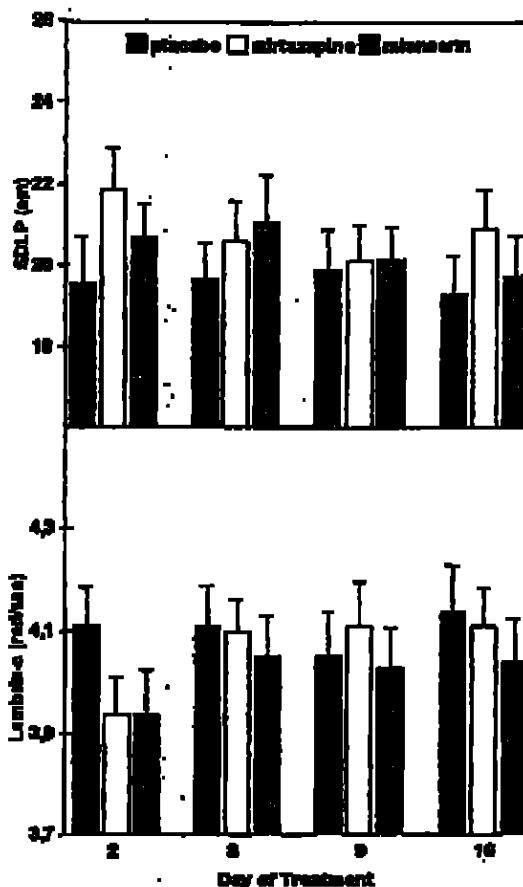


Figure 1. Mean (SE) EDLP (upper panel) and lambda-c (lower panel) adjusted for baseline on days 2, 8, 9 and 16 of treatment.

significance. CFF and CRT never differed between treatments.

Mood

The overall Treatment effect on alertness was always significant except on day 8. The effect of Treatment on contentedness was also significant on days 2 and 9. No effect of Treatment was found on calmness. Drug-placebo comparisons on separate days revealed decrements in alertness on all test days during treatment with mianserin. Mirtazapine also decreased alertness but its effects only approached significance on days 2, 9 and 16 of treatment. Contentedness decreased on day 2 and 9 of treatment with mianserin and on days 9

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Table 1. Summary of significant and nearly significant treatment effects on psychomotor and driving performance and mood as indicated by ANOVA (drug-placebo differences were always indicative of impairment)

Test	Day	df	ANOVA Overall		Mirtazapine vs placebo		Mianserin vs placebo	
			F	P	F	P	F	P
CFP (Hz)	2	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-
	9	-	-	-	-	-	-	-
	16	-	-	-	-	-	-	-
CTT (rad/s)	2	2.32	4.30	0.019	6.27	0.018	7.00	0.013
	8	-	-	-	-	-	-	-
	9	-	-	-	-	-	-	-
	16	-	-	-	-	-	-	-
CRT (ms)	2	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-
	9	-	-	-	-	-	-	-
	16	-	-	-	-	-	-	-
VIG (%)	2	-	-	-	-	-	4.43	0.043
	8	-	-	-	-	-	-	-
	9	-	-	-	-	-	-	-
	16	-	-	-	-	-	3.20	0.083
SDLP (cm)	2	2.32	3.07	0.060	6.00	0.020	-	-
	8	-	-	-	-	-	4.01	0.054
	9	-	-	-	-	-	-	-
	16	2.31	3.64	0.038	6.89	0.013	-	-
Alertness (mm)	2	2.32	4.30	0.024	3.37	0.076	8.30	0.007
	8	-	-	-	-	-	4.76	0.037
	9	2.32	4.05	0.027	3.18	0.084	7.59	0.010
	16	2.31	5.95	0.007	4.05	0.053	12.0	0.002
Contentedness (mm)	2	2.32	3.54	0.041	-	-	6.24	0.018
	8	-	-	-	-	-	-	-
	9	2.32	5.37	0.010	4.69	0.038	9.73	0.004
	16	-	-	-	4.31	0.046	-	-
Calmness (mm)	2	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-
	9	-	-	-	4.65	0.039	-	-
	16	-	-	-	-	-	-	-

and 16 of treatment with mirtazapine. Calmness decreased on day 9 of treatment with mirtazapine. An overview of all significant or nearly significant Treatment effects on performance and mood parameters is shown in Table 1.

Subjective sleep estimations

Both mirtazapine and mianserin increased estimated sleep duration over their entire period of administration ($\chi^2 = 36.12$ and 43.93 , respectively; $p = 0.000$). The separate drug effects on sleep duration were present, more or less constantly, within every successive 3-day period. Most

comparisons between periods of drugs and placebo treatment were significant. On the average, subjects slept 43.2 and 42.6 min longer during treatment with mirtazapine and mianserin than while taking placebo.

An apparent difference was noted between the drugs' effects on the group's impression of how well they had slept. Despite the increase in sleep duration, similar for both drugs, they rated their overall sleep quality as about the same with mirtazapine and somewhat worse with mianserin as compared to placebo. The latter difference was significant over all treatment nights ($\chi^2 = 19.45$; $p = 0.021$) and almost for the first three nights,

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MIRTAZAPINE AND MIANSERIN ON SLEEP AND DRIVING

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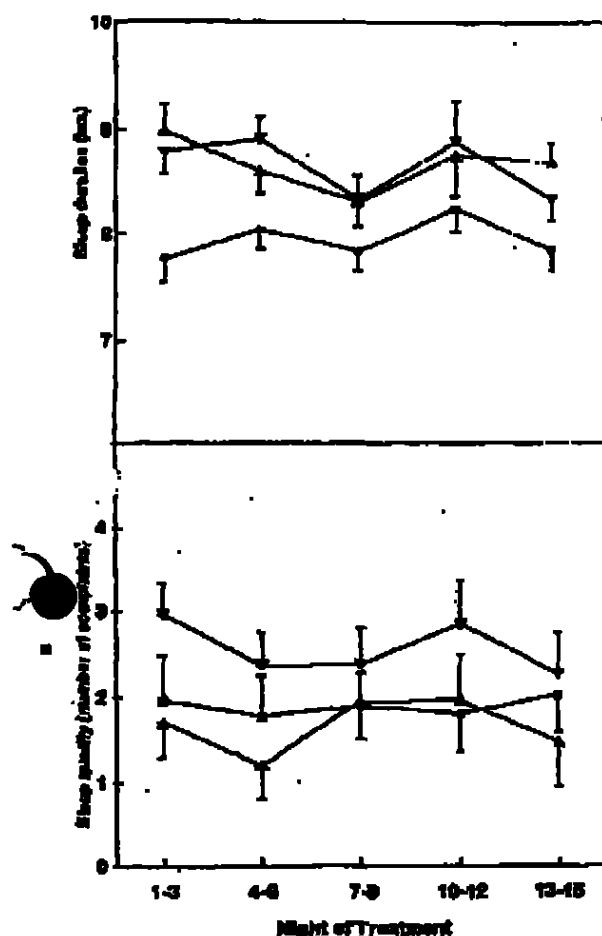


Figure 2. Mean (SE) sleep duration (upper panel) and sleep quality (lower panel) adjusted for baseline throughout every treatment period. Symbols indicate the following treatments: placebo, ■; mirtazapine, ●; mianserin, ▲.

tested separately ($Z = -1.88$; $p = 0.059$). Mean (SE) sleep duration and quality throughout every treatment condition are shown in Figure 2.

Subjective side-effects

The following self-rated side-effects significantly differed between each drug and placebo: drowsiness, weakness, memory disturbances, lethargy, headache, dry mouth, dizziness and concentration problems ($\chi^2 > 20.46$; $p < 0.015$). In addition, mianserin increased uncoordination and nausea ($\chi^2 > 27.89$; $p < 0.001$). Drug-placebo comparisons over successive 3-day intervals showed that

mianserin and mirtazapine similarly increased feelings of lethargy throughout treatment ($Z < -2.39$; $p < 0.016$); drowsiness (Figure 3) during four out of five intervals ($Z < -2.00$; $p < 0.045$); weakness between days 2 and 10 ($Z < -1.99$; $p < 0.046$) and difficulty concentrating between days 2 and 4 ($Z < -2.05$; $p < 0.039$). Dry mouth and dizziness were respectively greater than placebo levels between days 2-13 and 2-10 of mianserin treatment ($Z < -1.92$; $p < 0.055$) and between days 2-7 and 5-7 of mirtazapine treatment ($Z < -2.02$; $p < 0.043$). Headaches were more prevalent between days 8-13 of mianserin treatment ($Z < -2.11$; $p < 0.035$) and days 5-7 and 11-13 of mirtazapine treatment ($Z < -1.96$; $p < 0.049$).

Overall frequencies of spontaneously reported adverse events are summarized by treatment in Table 2. In total, 127 complaints were judged by the Medical Supervisor to be treatment-related. Multiple adverse events were reported by only one or two subjects within the same treatment periods. The types of events were similar after both drugs, but somewhat more frequent following mianserin. During mirtazapine treatment, adverse events reported by more than two subjects were: Fatigue (11x); drowsiness (12x), dry mouth (4x), cold, dizziness and difficulty concentrating (3x). During mianserin treatment they were: fatigue (17x), drowsiness (11x), dry mouth (6x), dizziness (5x), difficulty concentrating, tension in arms or legs (4x), and headache (3x). During placebo treatment there were few reports of adverse events, mainly headache (4x) and fatigue (3x).

Pharmacokinetics

Mean (SD) plasma concentrations for mirtazapine on respective treatment days were 6.55 (2.18), 11.87 (3.77), 17.86 (5.83) and 23.30 (9.99) ng/ml. Mean plasma concentrations (SD) of mianserin were 7.71 (3.02), 16.14 (9.66), 24.21 (12.80) and 35.39 (21.38) ng/ml.

DISCUSSION

The main purpose of this study was to determine whether ascending doses of mirtazapine and mianserin have any impairing effects on behaviour. Results from psychomotor and driving tests showed that impairment was most evident after the initial doses of mirtazapine 15 mg and mianserin 30 mg. On day 2, both drugs impaired

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Table 2. Treatment related adverse events as judged by the Medical Supervisor, rate of occurrence and numbers of subjects (%) complaining of each symptom in every treatment condition

	Mirtazapine	Mianserin	Placebo
Abdominal cramps		1 (5-56)	
Depressed		1 (5-56)	
Diarrhoea		1 (5-56)	
Difficulty concentrating	3 (18-75)	4 (22-22)	
Difficulty focusing eyes	1 (6-25)		
Difficulty waking up	1 (6-25)		1 (5-56)
Disturbance of equilibrium		1 (5-56)	
Dizziness	3 (18-75)	5 (27-78)	
Drowsiness	12 (75-00)	11 (61-11)	
Dry mouth	4 (25-00)	6 (33-33)	1 (5-56)
Fatigue (during daytime)	4 (25-00)	7 (38-89)	1 (5-56)
in the morning	3* (12-50)	3 (16-67)	
in the afternoon		1 (5-56)	
in the evening	4 (25-00)	6 (33-33)	2 (11-11)
Headache	1 (6-25)	3 (16-67)	4 (22-22)
Apathy		1 (5-56)	
Increased appetite	1 (6-25)		
Muscle spasms in legs	1 (6-25)		
in arms		1 (5-56)	1 (5-56)
Nausea	2 (12-50)	1 (5-56)	
Pain in legs		1 (5-56)	
in arms		1 (5-56)	
Palpitations	1 (6-25)		
Tension in legs		3 (16-67)	
in arms	1 (6-25)	1 (5-56)	
Shakiness	2 (12-50)	2 (11-11)	
Vomiting		2 (11-11)	
Muscular weakness		1 (5-56)	
Catch a cold	3 (18-75)		1 (5-56)
Sore throat	1 (6-25)		
Flu symptoms		1 (5-56)	
Loss of interest		1 (5-56)	
Weight gain		1 (5-56)	
Intracranial pressure		1 (5-56)	
Total complaints	48 (37-80)	69 (54-35)	10 (7-87)
Total subjects complaining of any symptom	14 (87-50)	17 (94-44)	7 (30-39)

*This complaint was reported by the same subject twice. Other complaints were reported only once per subject per treatment.

tracking performance, whereas driving and vigilance performance deteriorated after treatment with mirtazapine and mianserin respectively. All mean differences, however, were very small. The increase in SDLP of 2.2 cm after the first dose of mirtazapine was less than that shown by 'social drinkers' taking the test with a blood alcohol concentration (BAC) of 0.5 mg/ml (Louwerens *et al.*, 1987). This is an important comparison since epidemiological research has shown that BAC < 0.50 mg/ml is not associated with an elevated risk of fatal traffic accidents (Borkenstein *et al.*, 1964). The implication is that neither drug's effects

on driving performance in this study were of sufficient magnitude to reduce the safety of vehicle operation.

By day 8, little evidence of treatment effects were still present, although some driving impairment (increase in SDLP of 1.4 cm) could still be observed in the mianserin condition. Escalation of the dose did not affect performance on day 9. On day 16, however, mirtazapine and mianserin again produced some impairment, the former in the driving, and the latter in the vigilance test. Impairment on this day was still low in magnitude and not greater than the respective acute effects. These

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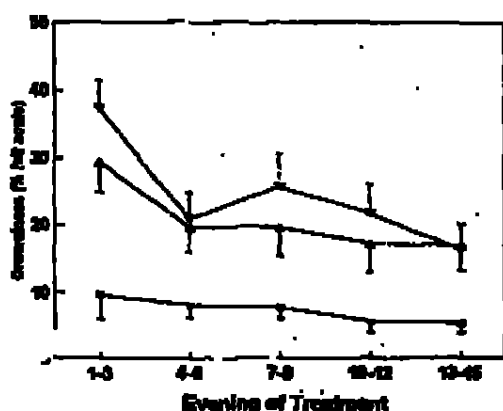


Figure 3. Mean (SE) drowsiness adjusted for baseline throughout every treatment period. Symbols indicate the following treatments: placebo, ●; mirtazapine, ■; mianserin, ▲.

results indicate that doubling the doses of both drugs after a week on medication produces no greater impairment than seen after the initial dose. Following these dosing regimens, mianserin and mirtazapine effects were always just above or below detection thresholds of comparably sensitive driving or psychomotor tests. For this reason one should pay less attention to the fact that both drugs affected performance in different tests at different times and more to the fact that both drugs impaired performance to the same extent throughout treatment. These effects cannot be ignored, but neither do they appear to be a source of special concern.

Mianserin's and mirtazapine's effects on performance in this study were clearly less in magnitude than those found previously. As mentioned in the Introduction, Mattila *et al.* rated the effects of a single dose of mirtazapine 15 mg on psychometric performance similar to those of amitriptyline 50 mg. Similarly, acute and repeated doses of mianserin 10 mg have been found to seriously impair psychomotor performance (Seppälä, 1977; Corran and Lader, 1986; Mattila *et al.*, 1978). Elevations in mean SDLP, three times as high as in the current study, have been found after administration of mianserin 10 mg tds by investigators employing the same driving test (Louwrens *et al.*, 1986; Ramsackers *et al.*, 1992). In the latter study, mean mianserin plasma concentrations prior to driving were almost the same (i.e. mean and range of 13, 7–18 mg/ml versus 8, 4–14) as those found in the current study. It is therefore very unlikely that mianserin's effects on driving performance in these studies are solely

attributable to differences in drug concentrations at the time of testing. Instead, the differences must be somehow related to the periods that elapsed between drug administration and performance testing.

Nocturnal doses of the sedating H_1 antagonist chlorpheniramine failed to affect driving performance of healthy volunteers when measured the next morning in the standard on-the-road driving test (Vermeiren *et al.*, 1998). These results could also not be explained by the drug concentrations at the time of testing, since chlorpheniramine possesses an elimination half-life of over 24 h. However, the use of a sustained release formulation appeared to contribute to the explanation of those results. Similarly, Ray *et al.* (1987) found no association between the use of sedating H_1 antagonists for promoting sleep and the risk of hip-fracture in an epidemiological survey. In another study, designed to measure the effects of the H_1 antagonist diphenhydramine, performance was initially impaired, but then recovered completely after a 60 min nap (Roehrs *et al.*, 1993). These results seem to indicate that H_1 blockade specifically activates sleep mechanisms which in turn may be reversed by sleep. Mianserin and mirtazapine are also known to produce sedation by H_1 receptor antagonism. Yet, in the current study, sleep apparently mitigated the drugs' sedative effects on psychomotor and driving performance in a similar, but as yet unknown, manner.

Mianserin and mirtazapine had comparable effects on mood, subjective feelings and sleep. Decrements in alertness, contentedness and an increment in sleep duration could be measured throughout treatments with both drugs. Self-rated side-effects were maximal at the beginning of treatment and perished over time. The magnitude of these side-effects were about the same for both drugs. Feelings of lethargy and drowsiness were pronounced in both drug treatments. These were accompanied by feelings of weakness, dry mouth and dizziness. Subjective feelings were more affected than objective performance, but this seems mainly due to the fact that the former were rated in the evening shortly after drug administration, and the latter were measured the next day. Spontaneously reported adverse effects were similar to side-effects just mentioned. During mirtazapine and mianserin treatment, adverse events that were reported most frequently were respectively: fatigue (11 and 17%), drowsiness (12 and 11%), dry mouth (4 and 6%), dizziness (3 and 6%) and difficulty

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concentrating (3 and 4×). The only difference between drugs was the total number of complaints; i.e. 48 during mirtazapine and 69 during mianserin treatment.

Objective and subjective results all converge on the fact that both mirtazapine and mianserin are mildly sedating throughout 2 weeks of treatment. Apparently, both drugs' sedating effects on daytime performance are much alleviated by nocturnal administering. Presumably, this is the reason why mirtazapine is currently recommended to be taken in single evening doses. Mianserin, on the other hand, is often prescribed as divided doses over the day. In our opinion, nocturnal dosing should be recommended for both drugs. This would not only promote their safety over days; it would also utilize their sleep-inducing properties for avoiding the occasional necessity for hypnotic coadministration.

ACKNOWLEDGEMENT

This study was supported by NV Organon, Oss, The Netherlands.

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European Journal of Clinical
Pharmacology
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Effect of the antidepressant Org 3770 on human sleep

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Received: July 24, 1989/Accepted in revised form: January 13, 1990

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Summary. The effect of a single dose (30 mg) of Org 3770 (mefizapine) on human sleep was assessed in a double blind, placebo controlled, cross over study in 6 young, healthy male volunteers. The sleep stage classification was based on visual scoring of 24 h electroencephalographic recordings according to the criteria of Rechtschaffen and Kales.

Org 3770 30 mg p.o. given 2 h before bedtime had a sleep promoting action in all subjects, resulting in a shorter time to the onset of sleep. Bedtime waking and dozing (Stage 1) were reduced in favour of deep, slow wave sleep (Stages 3 and 4). Org 3770 increased the latency of REM sleep with respect to Stage 2 sleep in all subjects. It also caused a minor reduction in waking periods during REM sleep and a lower frequency of awakenings after periods of movement. No effect of Org 3770 was observed in reaction and vigilance tests on the post treatment day.

The observed effects of Org 3770 on normal human sleep suggest that it might ameliorate the sleep disturbances encountered in endogenous depression, which are characterized by a reduction in slow wave sleep, an increase in nighttime awakenings and shortening of REM sleep latency.

Key words: mefizapine (Org 3770), sleep, antidepressant, REM sleep, waking, deep sleep, post-treatment effects

Org 3770 (mefizapine or Remergon®) is a tetracyclic compound with antidepressant activity (Claghorn et al. 1987). Its pharmacological profile is characterized by strong presynaptic α -2 blockade, moderate antiserotonergic activity potent antihistamine (H1) activity, and no appreciable anticholinergic activity and no activity on synaptic reuptake of catecholamines (Nickolson et al. 1982, de Boer et al. 1988). Org 3770 predominantly affects serotonin receptors of the 5-HT₁, 5-HT₂ and 5-HT₃ subtypes, and it has low affinity for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1C} receptors (De Graaf, De Boer, Broekkamp, Vijverberg, personal communications).

Its antidepressant properties were also suggested by human pharmac-EEG studies (Fink and Irwin, 1982) and by activity in predictive animal models (O'Connor and Leonard, 1986). In an automated system for the analysis of drug effects on sleep in the rat (Ruigt et al. 1989a; 1989b), Org 3770 showed an antidepressant profile (Ruigt, unpublished), characterised by a reduction in REM sleep combined with an increase in the latency to the first occurrence of REM; an increase in quiet waking; a

strong increase in slow wave sleep at relatively low doses, which did not affect REM sleep, and a moderate reduction in slow wave sleep followed by a strong rebound increase at higher doses.

One of the most prominent symptoms in endogenous depression is a general sleep disturbance (Gillin et al. 1984), characterized by 1) an increased number of nighttime awakenings, 2) a shift of REM sleep towards the sleep onset period; and 3) a reduction in the amount of slow wave sleep. Most antidepressant compounds normalize these sleep disturbances. The effects of the new antidepressant drug Org 3770 on normal human sleep have now been studied and are reported here.

Subjects and methods

Subjects

The study was performed in 6 healthy male volunteers, aged 20 to 25 y. Written consent was obtained from each subject after he had been fully informed about the objective, methods and risk of the investigation, which had been approved by the local Ethics Committee. Before enrolment and at the end of the study each subject underwent a thorough physical examination, ECG, EEG, laboratory tests of haematological, hepatic, and renal function and an assessment of the medical history. Regular medication with drugs or regular use of alcohol in the last three months before the start of the study was not allowed. None of the volunteers admitted to abnormal or unusual sleep patterns in a sleep questionnaire. The volunteers were accompanied throughout the study by a well trained supervisor, who monitored possible behavioural effects of the treatment.

Design

The study was performed according to a double-blind, placebo-controlled cross over design, in which the volunteers were studied in two experimental sessions, separated by a washout period of 13 days. Two weeks before the first session, which also served to make the volunteers acquainted with the experimental procedure, baseline EEG, ECG, laboratory parameters and psychometric test scores were obtained. On each experimental session subjects received either 30 mg Org 3770 or placebo p.o. at 21.00 h, 1 h after the start of a 24 h EEG recording. At 23.45 h subjects had to be in bed and the lights were turned off. On the next day, at 07.45 h, subjects were awakened, if necessary, and blood was sampled at 09.00 h for determination of the plasma Org 3770 level. For assessment of carry-over drug effects psychometric tests were done at 11.00 h.

Recording and sleep scoring

Sleep recordings were made in a silent, air-conditioned room in the sleep laboratory of the Leiden Academic Hospital. The polygraphic sleep-wake EEG was recorded during the night and the following day by means of a Medilog 9000 ambulatory monitoring system (Or-

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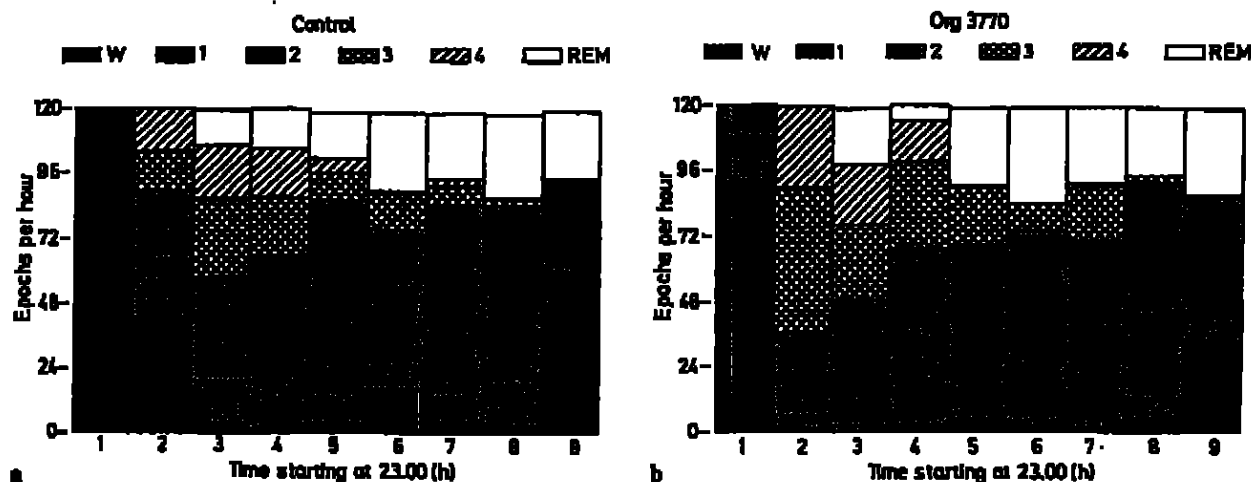


Fig. 1 a, b. Temporal distribution of sleep stages over 9 hours of the night-time recording period from 11.00 p.m. (a) under placebo conditions and (b) after ingestion of Org 3770. Bars do not always total 120 epochs, because some epochs were affected by movement artefacts

ford Medical), modified by Kemp (1967). The EEG was recorded from F_p-C_4 and P_2-O_2 with a grounding electrode at C_4 (Van Sweden et al. 1990). The electrooculogram was recorded from the outer canthus of each eye referred to the mastoid area. Electromyographic activity was recorded from the submental muscles. Polygraphic recordings were scored visually in 30 s epochs according to the criteria of Rechtschaffen and Kales (1968) by two independent raters, and the final score was based on consensus between them (Kemp and Kamphuisen, 1986). Apart from the standard sleep parameters, the following parameters were defined: "intermittent waking", all night time waking episodes preceded and followed by sleeping episodes; "light sleep", sleep Stages 1 and 2; "deep sleep", sleep Stages 3 and 4 combined; "arousals", transitions to waking or

Stage 1; "REM latencies 0, 1 and 2", respectively, latencies from lights off, from the first Stage 1 epoch and from the first Stage 2 epoch to the first REM epoch; all other latencies were calculated from the moment the lights were turned off (23.45 h).

Analysis

Apart from total analyses of the data over the bedtime and daytime periods data were calculated for each hour between 23.00 h and 08.00 h of each bedtime recording period. All statistical comparisons between Org 3770 and placebo were based on a (two-tailed, Student's) *t*-test. Sleep parameters were calculated directly from the individual hypnograms or from the individual sleep stage transition matrices.

Individual transition matrices were averaged separately for placebo and Org 3770 recordings and the average values were used to construct similarity matrices and diagrams, representations of the strength with which the different sleep stages were associated with each other in time. Preferential direction indices were made to indicate the predominant sequences in which two sleep stages occurred. Similarity values and preferential direction indices for example stages *a* and *b* were calculated according to the following formulae:

$$\text{Similarity} = 0.25 \left(\frac{\text{Trans } a \rightarrow b}{\text{Trans from } a} + \frac{\text{Trans } b \rightarrow a}{\text{Trans from } b} + \frac{\text{Trans } a \rightarrow a}{\text{Trans to } a} + \frac{\text{Trans } b \rightarrow b}{\text{Trans to } b} \right)$$

$$\text{Preferential direction} = \frac{\text{Trans } a \rightarrow b - \text{Trans } b \rightarrow a}{\text{Trans } a \rightarrow b + \text{Trans } b \rightarrow a}$$

Results

No clinically relevant effects of Org 3770 or placebo were observed on sodium, potassium, creatinine, urea, glucose, SGOT, SGPT, total protein, LDH, gamma-GT, alkaline phosphatase, haemoglobin, haematocrit, leucocytes, differential blood count, thrombocytes, urine specific gravity or sediment. After ingestion of placebo and Org 3770 two subjects complained of "tummy feelings" in the legs. One subject showed some muscle rigidity for 45 min after Org 3770, which subsided over the succeeding hours.

Table 1. Hypnogram parameters over the 8 hour period in bed. Data are expressed in 30 s epoch counts or in numbers (transitions, ratios). Statistical testing was done with a two-tailed Student's *t*-test

parameter	Placebo Average (SEM)	Org 3770 Average (SEM)	signifi- cance
waking	124 (74)	18 (11)	$P < 0.01$
stage 1	94 (22)	51 (18)	$P < 0.01$
stage 2	419 (30)	482 (68)	NS
stage 3	99 (24)	167 (69)	$P < 0.05$
stage 4	62 (35)	69 (32)	NS
REM	153 (50)	174 (43)	NS
movement	12 (16)	9 (10)	NS
ratio REM/nREM sleep	0.24 (0.07)	0.23 (0.07)	NS
intermittent waking	62 (62)	13 (10)	NS
light sleep	512 (42)	533 (81)	NS
deep sleep	162 (48)	236 (99)	NS
total sleep	836 (74)	942 (11)	$P < 0.01$
idem, excl. stage 1	743 (90)	892 (25)	$P < 0.01$
latencies (see Methods)			
stage 1	50 (25)	2 (3)	$P < 0.001$
stage 2	89 (39)	16 (12)	$P < 0.01$
REM 0	243 (42)	225 (42)	NS
REM 1	193 (51)	225 (42)	NS
REM 2	154 (32)	210 (48)	$P < 0.05$
transitions			
REM episodes	12 (8)	10 (4)	NS
REM arousals	9 (8)	5 (4)	NS
non-REM arousals	17 (12)	10 (6)	NS
total transitions	177 (31)	180 (40)	NS

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Physical and neurological examination did not reveal any abnormalities in any of the subjects, nor were any abnormalities found in the EEG and ECG. By 14 hours after administration Org 3770 did not have any significant effect on psychometric scores in an unprepared simple reaction time test, a four choice serial reaction time test or a vigilance test.

Sleep

The effect of a single oral dose of 30 mg Org 3770 on sleep is shown in Table 1 and Fig. 1. Org 3770 reduced the time spent waking in bed and the latency between going to bed and the onset of sleep. There was a clear tendency towards a reduction in the number of night time awakenings. Org 3770 not only augmented sleep, but it also deepened sleep, as shown by the increase in Stage 3 sleep and the concurrent reduction in stage 1 sleep. The compound did not significantly affect the absolute latency between going to bed and the first REM period. However, taking into account the early sleep onset after treatment, it is not surprising that Org 3770 did increase the latency between the onset of sleep and the first REM sleep period. The sleep-inducing effects of Org 3770 were significantly stronger in those subjects who showed more bed time waking during the placebo night ($p = 0.0001$, $df 1,4$; corr. coeff. -0.99 ; linear regression). There was also a trend indicating that the shorter the REM latency under placebo conditions the larger the increase in REM latency after administration of Org 3770 ($p = 0.12$, $df 1,4$; corr. coeff. -0.70).

The most marked changes due to Org 3770 were observed at the beginning and the end of the bedtime recording period (Fig. 1). The reduction in sleep latency already mentioned is consistent with the decrease in waking and the increase in lightsleep during the first hour. The deepening of sleep after Org 3770 is best seen during the second hour, as a clear increase in Stage 3 sleep. During the last hour of the time in bed there was a reduction in waking after Org 3770. During the daytime most of the subjects stayed awake. Two subjects on placebo and one subject on Org 3770 showed a few minutes of Stage 1 sleep around 12.00 h. One subject on Org 3770 took a daytime nap dominated by Stage 2 sleep for approximately 15 min at 12.15 h.

Sleep structure

Both the percentage duration of each sleep stage and their temporal distribution are important in evaluating the effects on sleep of psychotropic drugs. If compounds change the structure of sleep by changing the sequence in which the different stages normally occur, this may be an even more important drug action. Such changes can be inferred from analysis of the sleep stage transition matrices (Table 2a). The reduction shown in waking and Stage 1 sleep was associated with fewer transitions to these stages, suggesting that the length of individual bouts of waking and Stage 1 sleep had not been greatly affected. This was also true for the subsequent increase in Stage 3 sleep. The transition matrices during placebo and Org 3770 thus par-

Table 2. Sleep parameters derived from the individual transition matrices over the 8 h period bed (see Methods). The data to the left of the dividing bars represent the placebo group, and the data to the right represent recordings after Org 3770

a) Average sleep stage transition matrices (placebo/Org 3770)									
Stage	Waking	1	2	3	4	REM	Movement	Total	
Waking	-	188	171	00	00	00	00	199	
1	9/3	-	22/11	00	00	7/4	1/0	39/14	
2	6/3	9/5	-	25/13	0/1	5/5	5/5	50/41	
3	1/0	1/0	22/40	-	11/16	0/0	1/2	36/59	
4	0/0	0/0	1/1	12/15	-	0/0	0/0	13/17	
REM	2/2	7/3	2/3	0/0	0/0	-	1/2	12/10	
Movement	1/1	4/1	4/6	0/1	0/0	0/1	-	9/8	
total	199	39/18	52/51	37/29	11/17	12/10	8/9	178/180	

b) Similarity matrices (placebo/Org 3770)									
Waking									
Waking	1	2	3	4	REM	Movement	1	2	3
1	0.53/0.46	-	-	-	-	-	-	-	-
2	0.12/0.12	0.35/0.29	-	-	-	-	-	-	-
3	0.03/0.01	0.01/0.01	0.55/0.69	-	-	-	-	-	-
4	0.01/0.01	0.03/0.03	0.02/0.03	0.63/0.60	-	-	-	-	-
REM	0.07/0.13	0.37/0.38	0.18/0.23	0.00/0.01	0.00/0.00	-	-	-	-
Movement	0.04/0.03	0.15/0.08	0.31/0.34	0.04/0.08	0.02/0.03	0.07/0.12	-	-	-

c) Preferential direction for the transitions between the various classes (placebo/Org 3770)

Waking									
Waking	1	2	3	4	REM	Movement	1	2	3
1	0.33/0.34	-	-	-	-	-	-	-	-
2	-0.80/-0.74	0.43/0.42	-	-	-	-	-	-	-
3	-	-	0.07/0.04	-	-	-	-	-	-
4	-	-	-	-0.01/0.04	-	-	-	-	-
REM	-1.0/-0.85	0.00/0.09	0.36/0.30	-	-	-	-	-	-
Movement	-	-0.68/-0.73	0.17/-0.10	0.71/0.57	0.36/0.34	-	-	-	-

Stage transitions for which the similarity values are below 0.05 are not included, since the calculated preferential direction measures for such transitions are not meaningful

alleled the general changes induced by Org 3770 in the contribution of the different stages to the sleeping period.

Using transition matrices for deriving changes in sleep structure is complicated by the fact that changes in cell frequencies in the matrices often reflect general changes in the row or column totals (the general occurrence of a sleep state) rather than changes in sleep structure, i.e. changes in the probability that a particular sleep state will pass into some other sleep state. To correct for the changes in row and column totals, similarity matrices were derived (Table 2b). The similarity diagrams show that there was not much change in the strength with which the various sleep stages were associated with each other. The strongest effects observed after Org 3770 were a reduction in the association between Stage 1 sleep and REM sleep, between Stage 1 sleep and Stage 2 sleep and between Stage 1 sleep and movement and an increased association between Stage 2 sleep and Stage 3 sleep. The transitions between REM sleep and Stage 1 did not show any preferential direction, indicating that the transitions were due to Stage 1 interruptions of REM sleep, which appeared to occur less frequently after Org 3770. The preferential direction matrix also indicated that periods of movement during sleep frequently passed into Stage 1 sleep. Such transitions to Stage 1 sleep occurred less frequently after Org 3770 than placebo and appeared to occur instead during Stage 2 sleep.

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Discussion

The new antidepressant drug Org 3770 was shown here to affect sleep in human volunteers, causing deepening of sleep, shortening of sleep latency, a reduction in night time waking and an increase in the latency between sleep onset and the first REM sleep epoch. These changes suggest that the drug might ameliorate the sleep disturbances in depression, which are characterized by a reduction in deep slow wave sleep, accompanied by a reduction in low frequency energy in the EEG, an increase in night time awakenings and a shift in the occurrence of REM sleep from early in the morning to early at night, which is associated with a reduction in the latency between falling asleep and the first REM sleep period (Gillin et al. 1984). Short REM latency is considered one of the best biological markers of depression (Kupfer, 1976). Many antidepressant drugs selectively suppress REM sleep to a significant degree (Vogel, 1983). Selective REM sleep deprivation, not by medication but by awakening of the patients as soon as they enter REM sleep, has been reported to produce a pronounced and prolonged antidepressant effect (Vogel et al. 1980). It has been suggested from such data that the sleep abnormalities found in depression are not epiphenomena of the mood disorder but that they may be directly linked to the disease.

In sleep studies in rats, Org 3770 was found to act like mianserin (Ruigt, unpublished). The changes found consisted of an increase in quiet waking, an increase in REM latency, a shift of REM sleep from early to late in the sleeping period of the animals, and a bimodal effect on slow wave sleep, consisting of an early reduction and a late increase, which was especially prominent after low doses (Ruigt et al. 1988). Apart from the increase in deep sleep, similar changes have been observed in rats after the administration of a range of clinically active antidepressant compounds (van Delft et al. 1988).

The neurochemical basis or neuroanatomical substrate for the sleep effects of antidepressants, as well as for the sleep disturbances in depression, are still unknown. The advancement of REM sleep seen in depression may tentatively be attributed to a cholinergic facilitation or to a blockade of noradrenergic transmission, which is consistent with two models for the generation of REM sleep (Karczmar et al. 1970; McCarley and Hobson, 1975). Org 3770, in contrast to many other antidepressant compounds, does not have strong anticholinergic activity, but it does facilitate noradrenergic neurotransmission by inhibition of presynaptic modulatory α -2 receptors, while having virtually no effect on noradrenaline reuptake (de Boer et al. 1988). The deepening of sleep after Org 3770, as shown by the reduction in Stage 1 and the increase in Stage 3 sleep, may be related to its 5-HT₁ receptor antagonism, as other 5-HT₁ blockers, such as ritanserin, also increase slow wave sleep (Idzikowski et al. 1989).

Acknowledgements. We thank Dr. J. Moors for his critical reading of the manuscript, Messrs G. Keulen-Nelissen and M. v. Loosbroek for their laboratory assistance, G. v. d. Laar for general assistance during the trial and P. v. Haalen and E. Terlouw for their secretarial work.

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Pharmacology of Antidepressants: Selectivity or Multiplicity?

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The understanding of mechanisms of antidepressant action has evolved over time. The strong antidepressant activity of the tricyclic antidepressants (TCAs) has supported the role of both norepinephrine and serotonin (5-HT) in depression and the mechanism involved in antidepressant action. The next generation of antidepressants included the selective serotonin reuptake inhibitors (SSRIs), further supporting the role of serotonin, while the selective norepinephrine reuptake inhibitors such as maprotiline and reboxetine underlined the relevance of norepinephrine. These developments suggest that either facilitation of serotonin or norepinephrine or both may lead to an antidepressant response. The next step was the development of mixed serotonin-norepinephrine reuptake inhibitors (SNRIs), exemplified by venlafaxine and milnacipran. As with the TCAs, the antidepressant activity of SNRIs is based on inhibition of norepinephrine and serotonin reuptake, but unlike TCAs they do not have anticholinergic, antihistaminergic, and cardiotoxic effects. Although norepinephrine is known to stimulate serotonin cell firing rate via the α_1 -adrenoceptors, norepinephrine and serotonin have independent antidepressant actions. The latest development has been the introduction of the noradrenergic and specific serotonergic antidepressant mirtazapine. Its antidepressant effect appears to be related to dual enhancement of central noradrenergic and serotonergic neurotransmission by blockade of α_2 -adrenoceptors. In addition, mirtazapine directly blocks 5-HT₁ and 5-HT₂ receptors, which may account for its anxiolytic and sleep-improving properties as well as its lack of adverse events that are typical of SSRIs.

(J Clin Psychiatry 1999;60[suppl 17]:4-8)

The understanding of mechanisms of antidepressant action has evolved over time. In the 1960s, tricyclic antidepressants (TCAs) were found to act by inhibiting the reuptake of monoamines, especially serotonin (5-HT) and norepinephrine. However, TCAs also have other multiple pharmacologic properties that are held responsible for most of their side effects. The discovery that specific effects on monoamine uptake are important for antidepressant action led to the development of new antidepressants designed to be pharmacologically more selective. These new drugs included the selective serotonin reuptake inhibitors (SSRIs) and, more recently, a selective norepinephrine reuptake inhibitor (NRI). In general, these drugs have fewer serious side effects and are therefore better tolerated than the TCAs and monoamine oxidase inhibitors (MAOIs).

Recent studies, however, have challenged the notion that antidepressant selectivity is always better than multiple action. The latest antidepressants, including noradrenergic and specific serotonergic antidepressants (NaSSAs)

such as mirtazapine and serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and milnacipran, derive their therapeutic benefits from simultaneous action on both monoamine systems. In addition, by blocking specific serotonin receptors, antidepressants such as mirtazapine also reduce the undesired effects associated with SSRIs and SNRIs.

MODE OF ACTION

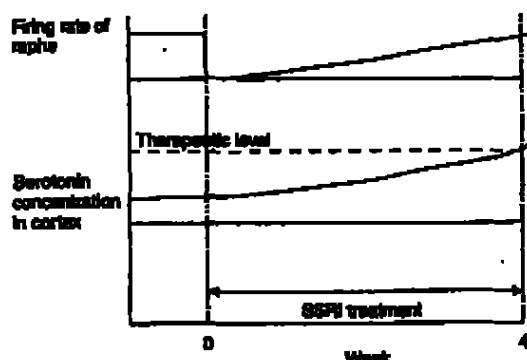
Antidepressants can be classified into 3 groups according to their principal mode of action: reuptake inhibitors, which inhibit monoamine uptake at the synaptic cleft; monoamine oxidase inhibitors, which inhibit monoamine degradation (e.g., moclobemide); and α_2 -adrenoceptor antagonists, which act at specific receptors to affect the monoamine system. Mirtazapine blocks the α_2 -adrenergic receptors, leading to an effect on both noradrenergic and serotonergic systems in the brain.¹ Reuptake inhibitors can be further divided into 3 categories: SSRIs, which are selective for serotonin (e.g., paroxetine); selective NRIs, which are selective for norepinephrine (e.g., reboxetine, TCAs); and SNRIs, which inhibit the uptake of serotonin and norepinephrine (e.g., venlafaxine, TCAs).

Reuptake inhibitors are categorized based on their relative potency to block the serotonin and norepinephrine uptake sites. SSRIs are more potent at the serotonin reuptake

From Utrecht Medical Center, Utrecht, the Netherlands.
Presented at the Scientific Expert Meeting, held in Monte Carlo, Monaco, February 26-27, 1999, and sponsored by NV Organon.

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Figure 1. Time Lag of SSRIs*



*Abbreviation: SSRIs = selective serotonin reuptake inhibitors.

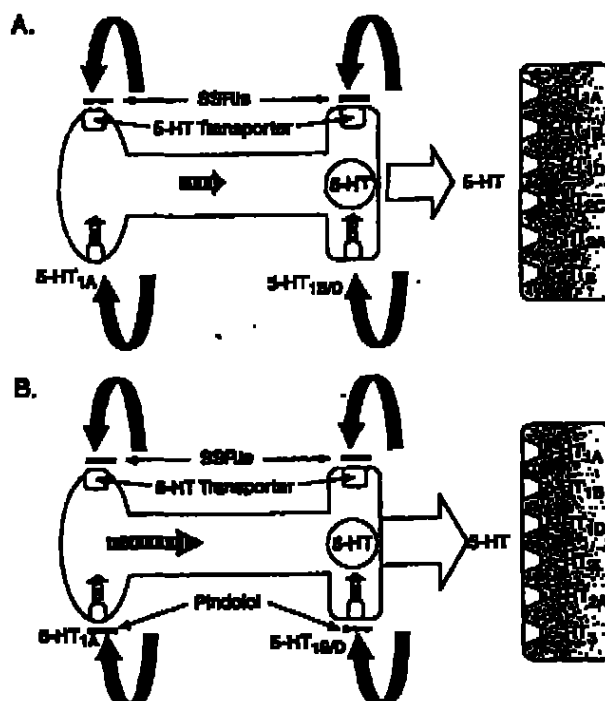
site, while selective NRIs more or less selectively inhibit norepinephrine uptake. SNRIs inhibit the reuptake of both monoamines to roughly the same extent. TCAs are generally classed as SNRIs or selective NRIs, but clomipramine is considered to be an SSRI, although its major metabolite is effective as a selective NRI. In addition to their effects on uptake mechanisms, TCAs have multiple other pharmacologic properties and thus are nonselective agents, whereas reboxetine and venlafaxine are both selective agents.

ONSET OF RESPONSE

Although blockade of reuptake occurs almost immediately upon administration of an SSRI, the clinical effect of reuptake inhibitors is delayed for 3 to 4 weeks (Figure 1). Microdialysis and electrophysiologic studies in animals have revealed that this delay in efficacy parallels the change in neuronal activity of the monoamine neurons. Reuptake inhibitors increase the release of serotonin and/or norepinephrine, but at the same time decrease neuronal activity (firing rate), which partly abolishes the effect on the release of serotonin or norepinephrine. However, with continued treatment, neuronal activity is restored, resulting in a gradual increase in serotonin release, which parallels clinical efficacy.

Figure 2 illustrates in detail the mechanisms operating in the serotonin system. Presynaptic 5-HT₁ autoreceptors play an important role in the regulation of both the release of neurotransmitter and neuronal activity of the neurons. Increased levels of serotonin in the cell body region activate the 5-HT_{1A} receptors. As a consequence, neuronal firing is decreased, resulting in a decrease of serotonin release. Activation of the 5-HT_{1B} receptors in terminal areas also attenuates the terminal release. These secondary effects of reuptake inhibitors nullify or at least substantially reduce the effect of these agents on serotonin release and

Figure 2. The Serotonergic Synapse*



*Increased serotonin in the cell body and terminal region, which is the product of SSRI activity, (A) activates 5-HT_{1A} and 5-HT_{1B} receptors, resulting in decreased serotonin release in the terminal region and a decreased firing rate in the cell body region and thus reduced clinical response. The addition of drugs such as pindolol (B) that block 5-HT_{1A} and 5-HT_{1B} receptors can hasten clinical response to SSRIs.

reduce the immediate clinical response. With long-term treatment, these inhibitory receptors become less sensitive, resulting in a gradual attenuation of the restraining effects and an increase of serotonin release in the brain. This increase parallels clinical efficacy.

If this explanation of the delay in onset of efficacy with reuptake inhibitors is correct, one would expect drugs that block these receptors to hasten the clinical response. Pindolol can block both 5-HT_{1A} and 5-HT_{1B} receptors. In animals, pretreatment with this drug significantly stimulates serotonin release in the cortex, but clinical data are as of yet equivocal. However, some investigators have reported a hastening and augmentation of the effect of SSRIs.² These data do suggest that drugs capable of blocking neurotransmitter release by controlling receptors may have clinically relevant effects.

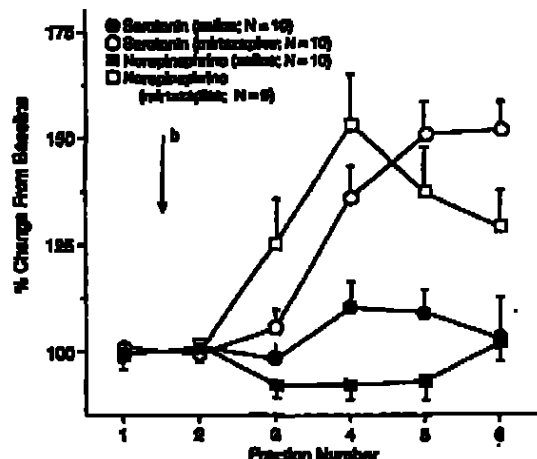
MIRTAZAPINE

Mirtazapine is a new antidepressant with a novel mechanism of action. It has been shown to block norepinephrine release by controlling α_2 -autoreceptors in the brain. In

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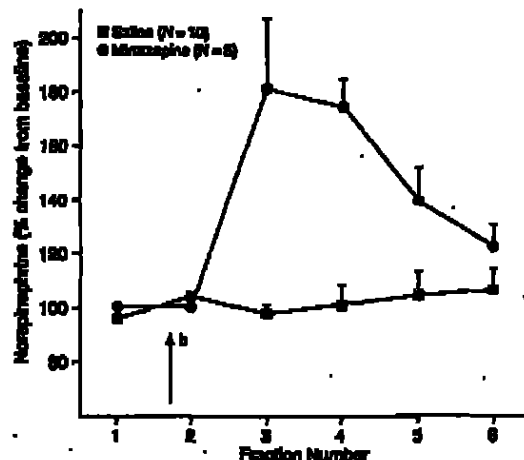
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Figure 3. Effect of Mirtazapine on Serotonin and Norepinephrine Release in the Hippocampus^a



^aData from reference 3. Samples were collected for 30 minutes. Values are mean (SEM).
^bPoint of administration.

Figure 4. Effect of Mirtazapine on Norepinephrine Release in the Locus Cereuleus^a



^aData from reference 3. Samples were collected for 30 minutes. Values shown as mean (SEM).
^bPoint of administration.

Table 1. Summary of Affinity of Antidepressants for Various Receptors^a

Antidepressant	α_1 -Adrenoceptors (K _d)	α_2 -Adrenoceptors (K _d)	5-HT _{2A} Receptors (K _d)
Mirtazapine	100	400	10
Mianserin	73	34	7
Venlafaxine	> 10,000	> 10,000	> 10,000
SSRIs	> 4000	> 3000 ^b	> 4000 ^c
TCA's	> 3000 ^d	20-80	20-120

^aData from references 4-7. K_d is the equilibrium dissociation constant, in nM. Abbreviation: 5-HT = serotonin, TCA's = tricyclic antidepressants.

^bN.B. paroxetine = 380.

^cN.B. fluoxetine = 210.

^dN.B. amitriptyline = 630.

microdialysis studies have shown that mirtazapine has a dual mode of action that increases both norepinephrine and serotonin levels in the brain. Although attained by different mechanisms, the effect of mirtazapine on monoamine release resembles that of the SNRIs at high doses. In addition, mirtazapine also blocks 5-HT₂ and 5-HT₁ receptors, activation of which is held responsible for many of the undesired effects of SSRIs and SNRIs. Figure 3 illustrates the effect of mirtazapine on both serotonin and norepinephrine release in rat hippocampus in vivo.³ Upon administration of mirtazapine, both norepinephrine and serotonin levels are elevated to almost the same extent, demonstrating mirtazapine's dual effect.

Mirtazapine is unique in that it has a clinically relevant affinity for the α_2 -adrenoceptor (Table 1).⁴⁻⁷ Mianserin is virtually the only other antidepressant to have this property, although mianserin also binds to the α_1 -adrenoceptor.⁸ Mir-

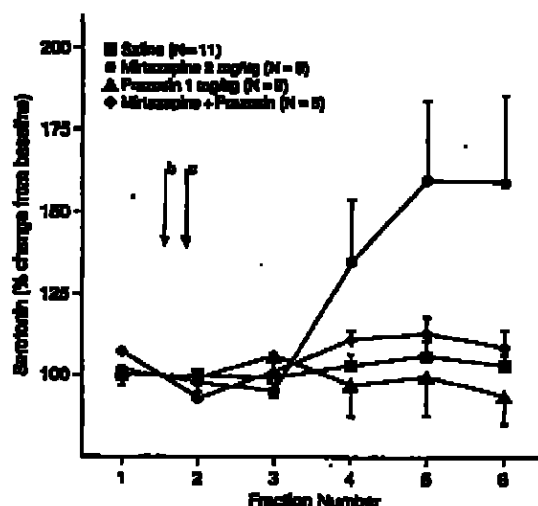
tazapine has no appreciable effect on the α_1 -adrenoceptor, whereas it has an affinity for 5-HT_{2A} receptor similar to that of mianserin and other TCAs. Mirtazapine is the only antidepressant capable of blocking the 5-HT₂ receptor.

Mirtazapine's main action is the blockade of the α_2 -adrenoceptors, which should enhance the release of norepinephrine in the brain since these receptors control the firing rate (in cell body region) and the release (in the terminal region) of norepinephrine. Because the effect results from the blockade of the release-inhibitory receptors, one would not expect this effect to be delayed. A measurement of the release of norepinephrine in the locus ceruleus, the principal cell body region of the noradrenergic system, was used to assess the effect of mirtazapine on the neuronal firing rate, since increased neuronal activity is reflected by an increase in norepinephrine release in that region (Figure 4).³ The data show that acute administration of mirtazapine significantly elevates the neuronal activity of the noradrenergic system, resulting in an increase in the norepinephrine release in the cortex.

To fully understand the effect of mirtazapine on the serotonergic system, we must take into account the neuronal cross talk between the 2 monoamine systems. Firstly, noradrenergic fibers impinge on serotonergic cell bodies in the raphe region. Norepinephrine released in the serotonergic cell body region stimulates the serotonergic firing through α_1 -adrenoceptors located on these cell bodies. Since mirtazapine leaves this receptor unaffected, it is expected to stimulate the serotonin firing rate and as a consequence, serotonin release in the brain. Secondly, norepinephrine, which is released in the hippocampus and other brain regions, inhibits serotonin release through α_2 -heteroreceptors

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Figure 5. Effect of Mirtazapine and Prazosin on Serotonin Release in the Median Raphe Nucleus^a

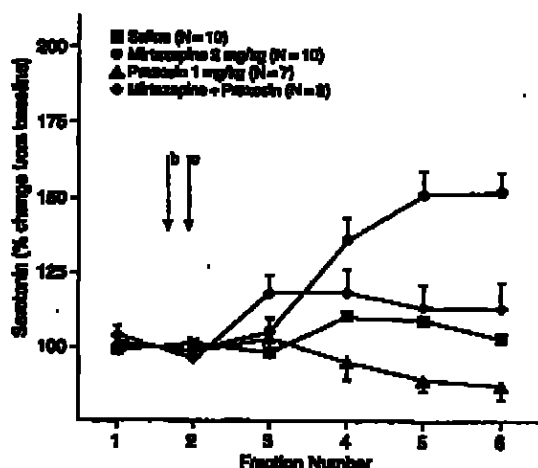


^aData from reference 3. Samples were collected for 30 minutes. Values shown as mean (SEM).

^bPoint of administration for prazosin or saline.

^cPoint of administration for mirtazapine or saline.

Figure 6. Effect of Mirtazapine and Prazosin on Serotonin Release in the Hippocampus^a



^aData from reference 3. Samples were collected for 30 minutes. Values shown as mean (SEM).

^bPoint of administration for prazosin or saline.

^cPoint of administration for mirtazapine or saline.

located on serotonin neuron terminals. Mirtazapine also blocks α_2 -heteroreceptors at this neuronal site, reinforcing the effect on the firing rate and subsequent serotonin release in those areas where this interaction is present.

To further investigate the importance of α_1 receptor stimulation on mirtazapine's mechanism of serotonin re-

Table 2. Side Effects Associated With the Stimulation of Different Neurotransmitter Systems^a

5-HT (overall)
Nausea
Migraine
Gastrointestinal problems
Sexual dysfunction
Norepinephrine
Tachycardia
Tremor
Potentiation of sympathomimetics
5-HT receptors
5-HT ₁
Hypophagia
5-HT ₂
Irritability
Nervousness
Insomnia
Sexual dysfunction
5-HT ₃
Nausea
Vomiting
Other neurotransmitter systems
Histamine H ₁
Sedation
Weight gain
Muscarinic
Dry mouth
Blurred vision
Confusion (elderly)
Constipation
Tachycardia
Urinary retention
α_1 -Adrenergic
Postural hypotension
Reflex tachycardia
Potentiation of antihypertensives
Drowsiness
Dizziness

^aBased on references 4 and 9.

lease, the effect of the addition of prazosin was studied. Prazosin is an antihypertensive agent that is a selective α_1 -adrenoceptor blocker. As seen in Figure 5, mirtazapine significantly enhanced serotonin neuronal activity.³ Prazosin itself had virtually no effect on serotonin activity, but was able to block the effect of mirtazapine almost completely. The effect of mirtazapine and prazosin addition on serotonin release in the hippocampus is shown in Figure 6.³ Mirtazapine increases the serotonin release, primarily through stimulation of α_1 -adrenoceptors, located on serotonin cell bodies, and addition of prazosin attenuates this effect.

Side Effects

Stimulation of the serotonergic and noradrenergic systems plays a crucial role in the mechanism of action of antidepressants; however, one may also expect some associated side effects. Some of the frequently observed side effects related to the stimulation of various neurotransmitter systems in the brain are shown in Table 2.^{4,9} The affinities of various antidepressants to these neurotransmitter systems are shown in Table 3. TCAs have high affinity for

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Table 3. Affinity of Antidepressants for the Histamine H₁, Muscarinic, and α_1 -Adrenergic Receptors^a

Antidepressant(s)	Histamine H ₁	Muscarinic	α_1 -Adrenergic
Mirtazapine	++	-	-
Mianserin	++	-	++
Venlafaxine	-	-	-
SSRIs	-	-	-
TCA _s	+	++	+

^aSymbolic: ++ = high, + = moderate, - = low.

histamine H₁, muscarinic, and α_1 -adrenergic receptors, leading to a wide range of undesirable side effects. However, selectivity of pharmacologic action on a single neurotransmitter system does not necessarily equate to fewer side effects. Given the global effect of serotonin on brain function and the large number of receptors involved, one may expect an array of side effects. In particular, stimulation of 5-HT₂ and 5-HT₁ receptors is associated with some of the undesired effects of the SSRIs and the SNRIs, such as nausea and insomnia. Blocking these receptors may lower these side effects, leading strength to the theory that specific multiplicity of action could have an advantage over selective action. In addition to its global effect on serotonin release, mirtazapine also blocks the 5-HT₂ and 5-HT₁ receptors and therefore is associated with fewer adverse effects related to the stimulation of these receptors. In addition, it is free of muscarinic and α_1 -adrenergic side effects.¹⁰

CONCLUSIONS

In conclusion, mirtazapine is a new dual-acting antidepressant with a novel mechanism of action. It enhances noradrenergic and serotonergic neurotransmission but

blocks 5-HT₂ and 5-HT₁ receptors. Like the SNRIs, it enhances the availability of both norepinephrine and serotonin, but has a different mechanism of action that should preclude any delay in the onset of clinical efficacy. In contrast to the SSRIs and the SNRIs, its effect on the serotonin system is specific by virtue of its 5-HT₂ and 5-HT₁ blocking properties, resulting in better tolerability.

Drug names: mirtazapine (Elevil) and others; citalopramine (Anafanil and others), fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil), pindolol (Visken), prazosin (Minipress and others), sertraline (Zoloft), venlafaxine (Effexor).

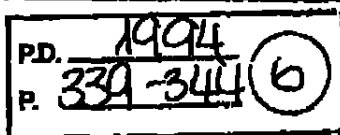
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ORIGINAL RESEARCH ARTICLE

Drug Inven. 2 (2): 339-344, 1994
0114-9432/94 2006-0539/943.00/0

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XP-000981393

Mirtazapine, a Novel Antidepressant, in the Treatment of Anxiety Symptoms

Results from a Placebo-Controlled Trial

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Summary

In order to assess the efficacy and tolerability of mirtazapine (Org 3770), 40 outpatients with a primary diagnosis of anxiety states [International Classification of Diseases (ICD-9)] were treated in a randomised, double-blind, placebo-controlled, 4-week study (mirtazapine, $n = 20$; placebo, $n = 20$). Daily dosages of mirtazapine were 15 to 25mg. The dosage could be titrated upwards or downwards by 5 mg/day, depending on the clinical response or the development of adverse events, respectively. Anxiety symptoms were assessed at baseline and after 7, 14, 21 and 28 days of treatment using the Hamilton Anxiety Scale (HAMAS) and the Zung Anxiety Scale (ZAS); global functioning was assessed by the Global Assessment Scale (GAS). Biochemical, haematological and urinary variables were also measured. After 28 days of treatment, mirtazapine-treated patients experienced significantly greater improvement from baseline in overall anxiety symptoms and psychic anxiety (assessed by HAMAS and ZAS scores) and in global functioning (assessed by GAS scores) than placebo-treated patients. There were no clinically significant changes in biochemical, haematological or urinary variables with either treatment. Mirtazapine was well tolerated; only one patient withdrew from the study because of adverse events. Sedation was experienced significantly more often by mirtazapine-treated patients, while placebo-treated patients complained significantly more often of insomnia and crying, and had more sleep disturbances. In this study, mirtazapine appeared to be an effective and well tolerated treatment for patients with anxiety symptoms as a primary complaint.

Mirtazapine is a new antidepressant with a substantially different pharmacological profile from that of both the tricyclic antidepressants and selective serotonin reuptake inhibitors. It is a specific antagonist of presynaptic α_2 -adrenoceptors, and only marginally affects α_1 -adrenoceptors. The blockade of presynaptic α_2 -adrenoceptors causes an increase in the release of noradrenaline. The subsequent activation of α_1 -adrenoceptors, which

mediate serotonergic neuronal cell firing, and the direct activation of inhibitory α_2 -adrenoceptors located on serotonergic nerve terminals leads to an increase in the release of serotonin (5-HT). However, the effects of released 5-HT are only exerted via 5-HT₁ receptors, since 5-HT₂ and 5-HT₃ receptors are directly blocked by mirtazapine.^[1-3]

The antidepressant activity and favourable tolerability of mirtazapine compared with other cur-

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rently used antidepressants has already been established.^[4-10]

Although anxiety and depressive disorders are usually regarded as distinct diagnostic categories,^[11,12] they frequently share common symptoms. In contrast, the 10th revision of the World Health Organization International Classification of Diseases (ICD-10) contains a diagnostic category of 'mixed anxiety and depressive disorder'.^[13] Importantly, about 33 to 40% of patients with major depression (DSM-III or DSM-III-R) also suffer from anxiety disorder (usually generalised anxiety disorder and panic disorder), and 30 to 50% of patients with anxiety disorder also meet criteria for major depression.^[14] Not surprisingly therefore, the antidepressant drugs have been extensively studied in the treatment of anxiety disorders.^[15,16]

The aim of this trial was to assess the efficacy and tolerability of mirtazapine, a proven antidepressant, in a 4-week, double-blind, randomised, placebo-controlled study in the treatment of outpatients with primary anxiety symptoms.

Patients and Methods

Patients

40 outpatients with a primary diagnosis of anxiety states in accordance with the 9th revision of the World Health Organization International Classification of Diseases^[17] were recruited into the study.

All patients gave informed consent to participate, and full ethical approval was obtained from the necessary committees and regulatory authorities. The study was performed in full accordance with the Helsinki Declaration.

At baseline, all patients had a score of ≥ 12 on the Hamilton Anxiety Scale (HAMAS).^[18] Exclusion criteria included: any progressive physical illness, organic brain syndrome, schizophrenia, primary depressive illness, hyperthyroidism, alcohol or drug abuse, risk of pregnancy or lactation, and the presence of 2 or more clinically significant abnormal laboratory parameters at screening. The

anxiety state was considered to be the primary psychiatric disorder at screening, while associated personality problems, or obsessional and hysterical features of secondary nature, did not result in exclusion.

In total, 22 patients (12 mirtazapine- and 10 placebo-treated patients) received treatment with benzodiazepines in the pretrial period.

Methods

Patients underwent a placebo washout period of up to 7 days before the start of the study. No other psychotropic medication was permitted except intermittent use of a nonbenzodiazepine hypnotic at night-time.

After a full physical examination and biochemical, haematological and urinary measurements, eligible patients were randomly allocated to treatment with mirtazapine ($n = 20$) or matching placebo tablets ($n = 20$) for 28 days. Mirtazapine therapy was initiated at 15 mg/day ($n = 10$) or 20 mg/day ($n = 10$) in 3 divided doses. During the course of the trial, dosages were titrated according to the individual patient's response, up to a maximum of 25 mg/day of mirtazapine, or 5 placebo tablets/day.

5 mg/day

Using the HAMAS and the self-rating Zung Anxiety Scale (ZAS),^[19] the severity of anxiety symptoms was assessed at baseline and after 7, 14, 21 and 28 days of treatment. At the same time-points, the patient's global functioning was assessed by Global Assessment Scale (GAS) scores.^[20] Biochemical, haematological and urinary variables were measured at baseline and after 28 days. Adverse events were recorded weekly.

Statistical Methods

An analysis of covariance was applied to the somatic, psychic and total anxiety scores of the HAMAS and ZAS, and total GAS score. Analyses were performed for day 28 only, using the baseline values as covariable. The 95% confidence intervals were determined for the difference in mean values between mirtazapine and placebo. The HAMAS insomnia and depression items were analysed

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Table I. Patient characteristics at baseline

	Mirtazapine (n = 20)	Placebo (n = 20)
Gender		
Female	12	15
Male	8	5
Age (y)	21-52	25-59
Weight (kg)	49-89	49-88
Rating scale scores (mean $\pm$ SEM)		
HAMAS (total)	24.2 $\pm$ 0.6	24.7 $\pm$ 0.9
ZAS (total)	26.1 $\pm$ 0.8	25.8 $\pm$ 0.8
GAS	43.5 $\pm$ 0.8	43.2 $\pm$ 0.9

Abbreviations: GAS = Global Assessment Scale; HAMAS = Hamilton Anxiety Scale; ZAS = Zung Anxiety Scale.

Patients who withdrew from the study for various reasons before the end of the second week of treatment were not included in the statistical analysis.

Results

Demographic Data

40 outpatients (13 females, 27 males), aged 21 to 59 years, with a primary diagnosis of anxiety states (ICD-9), were randomly assigned to treatment with mirtazapine or placebo. Baseline demographic data, including rating scale scores, are summarised in table I. The treatment groups were well matched for baseline demographic characteristics and mean group rating scale scores.

Withdrawals

Four patients, 2 from each treatment group, withdrew from the study. One patient in the

using the Yates test at the end of treatment. The frequencies of adverse events were analysed on day 28 using a χ^2 -test.

All statistical tests were 2-sided, and a p value <0.05 was considered statistically significant.

Table II. Mean daily dosages of mirtazapine and placebo during 4 weeks of treatment

Group	Statistics	Week 1	Week 2	Week 3	Week 4
Mirtazapine (mg/day)	Mean	17.5	18.5	19.0	17.5
	SD	± 2.5	± 2.0	± 3.0	± 2.5
	n	20	20	18	18
Placebo (tablets/day)	Mean	3.5	4.3	4.5	4.5
	SD	± 0.6	± 0.6	± 0.5	± 0.9
	n	20	18	18	20

Table III. Rating scale scores (group mean $\pm$ SEM) at baseline and after 28 days of treatment with mirtazapine and placebo

Rating scale	Mirtazapine		Placebo		Mean difference from placebo after 28 days' treatment (95% CI)
	baseline (n = 20)	day 28 (n = 18)	baseline (n = 20)	day 28 (n = 18)	
HAMAS score					
Total	24.2 ± 0.6	18.9 ± 0.9	24.7 ± 0.9	19.6 ± 1.3	-3.5* (-6.0, -0.9)
Somatic (sum of items 7-13)	8.4 ± 0.7	7.0 ± 0.7	9.1 ± 0.4	8.4 ± 0.7	0.0 (-0.2, 0.1)
Psychic (sum of items 1-6, 14)	16.1 ± 0.0	8.4 ± 0.7	15.4 ± 0.7	11.2 ± 0.7	-0.4* (-0.7, -0.2)
ZAS score					
Total	26.1 ± 0.8	18.8 ± 1.0	25.6 ± 0.8	20.3 ± 1.1	-3.5* (-6.0, -1.0)
Somatic (sum of items 6-8, 10-18)	10.6 ± 0.7	8.6 ± 0.6	11.3 ± 0.7	9.4 ± 0.7	-0.2 (-1.7, 1.2)
Psychic (sum of items 1-5, 9, 19-20)	15.8 ± 0.4	8.3 ± 0.6	14.3 ± 0.4	10.8 ± 0.5	-3.2* (-4.8, -1.6)
GAS score					
	43.5 ± 0.8	38.4 ± 1.3	43.2 ± 0.9	31.7 ± 1.8	7.8* (3.4, 12.4)

* p < 0.05 vs placebo.

Abbreviations: GAS = Global Assessment Scale; HAMAS = Hamilton Anxiety Scale; ZAS = Zung Anxiety Scale.

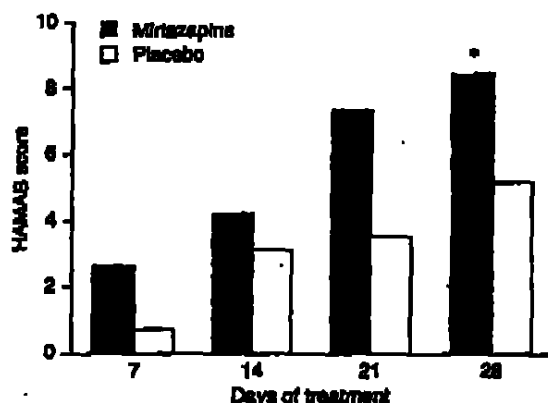
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Fig. 1. Improvement from baseline in total Hamilton Anxiety Scale (HAMAS) scores (group means) during 28 days of treatment with either mirtazapine or placebo. * $p < 0.05$; analysis of covariance: estimated treatment contrast mirtazapine minus placebo -3.5 , 95% confidence interval -6.0 to -0.9 .

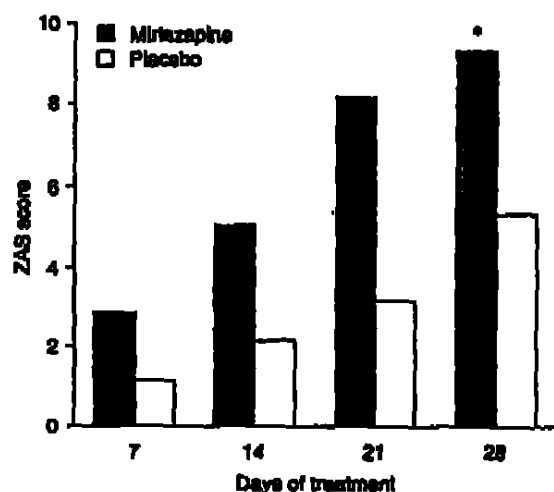


Fig. 2. Improvement from baseline in total Zung Anxiety Scale (ZAS) scores (group means) during 28 days of treatment with either mirtazapine or placebo. * $p < 0.05$; analysis of covariance: estimated treatment contrast mirtazapine minus placebo -3.5 , 95% confidence interval -6.0 to -1.0 .

mirtazapine group and 2 patients in the placebo group withdrew because of an inadequate treatment effect, and 1 mirtazapine-treated patient withdrew because of adverse experiences (e.g. fatigue, balance problems and cardiac symptoms).

Dosage

The mean dosages of study medication are shown in table II. While the mean dosages of mirtazapine remained relatively stable during the study period, the number of placebo tablets increased from a mean of 3.5 tablets/day during week 1 to 4.5 tablets/day during week 4 of the treatment period.

Clinical Efficacy

Table III summarises the mean scores on the HAMAS, ZAS and GAS rating scales, estimated score contrasts for the 3 parameters between mirtazapine and placebo, and the corresponding 95% confidence intervals.

Over 28 days of treatment, patients in both groups experienced an improvement in anxiety symptoms. However, the effect of mirtazapine on overall anxiety, psychic anxiety symptoms and global functioning (as assessed by HAMAS, ZAS and GAS scores) was significantly superior to that of placebo ($p < 0.05$; analysis of covariance). Figures 1 and 2 show improvements from baseline in the mean group total HAMAS and ZAS scores over 28 days of treatment with either mirtazapine or placebo.

The effect of mirtazapine on the HAMAS insomnia item was superior to that of placebo, reaching the borderline of significance at day 28 [0.61 and 1.17 for mirtazapine and placebo groups, respectively; $p = 0.051$ (Yates test)]. The two treatments had a similar effect on the HAMAS depressed mood item [1.50 and 1.78 for mirtazapine and placebo groups, respectively; $p = 0.12$ (Yates test)].

Tolerability

In general, both treatments were well tolerated. However, the adverse event profile shows differences between the treatments. After 28 days, crying and difficulty in falling asleep were significantly more frequent in placebo-treated patients. Furthermore, patients treated with placebo experienced repeated and early waking more frequently than mirtazapine-treated patients. Sedation was the only

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Table IV. Number of patients experiencing adverse events during treatment with mirtazapine or placebo

Adverse event	Mirtazapine		Placebo	
	week 1	week 4	week 1	week 4
Sedation	15*	13*	3	5
Crying	4	1	11	10†
Difficulty in falling asleep	10	1	14	8†
Dizziness	10	8	8	7
Repeated waking	7	3	8	8
Early waking	11	6	12	11
Dry mouth	5	2	4	4
Nausea	8	1	5	8

* $p < 0.05$ vs placebo; † $p < 0.05$ vs mirtazapine.

adverse event that occurred significantly more often in patients treated with mirtazapine than in those treated with placebo (table IV).

No clinically relevant abnormalities in biochemical, haematological or urinary variables were observed with either treatment.

Discussion

This placebo-controlled study set out to assess the efficacy and tolerability of mirtazapine, a new antidepressant, in outpatients with anxiety states. After 28 days of treatment, the differences between the 2 treatment groups were statistically significant in favour of mirtazapine for total and psychic anxiety scores on the HAMAS and ZAS, and the total GAS score, thus demonstrating that mirtazapine was superior to placebo in the reduction of anxiety symptoms and improvement of patient's global functioning.

The extent of improvement of the HAMAS insomnia item was greater with mirtazapine than with placebo after 28 days of treatment, reaching the borderline of significance. Improvements in the HAMAS depression item were similar in the two treatment groups. This may suggest that the beneficial effect of mirtazapine on anxiety symptoms is independent of its antidepressant actions.

Approximately half of the patients in each treatment group were treated with benzodiazepines in the pretrial period. It is possible that the mirtazapine-treated patients experienced fewer withdrawal symptoms than the placebo-treated ones, and con-

sequently had a more favourable outcome at the end of our study. However, it is unlikely that this was the case since similar numbers of patients in both treatment groups withdrew because of lack of efficacy (mirtazapine $n = 1$, placebo $n = 2$). Moreover, a gradual and continuous improvement from baseline was observed in both treatment groups throughout the study period.

Mirtazapine was well tolerated; only 1 patient withdrew from the study because of adverse events. Sedation was the only adverse event that occurred significantly more frequently with mirtazapine. Throughout the study period, placebo-treated patients complained significantly more often of crying and difficulty in falling asleep, and experienced repeated and early waking more frequently than mirtazapine-treated patients.

In the present study, mirtazapine, which has proven efficacy in depressed patients,^[4-10] has also been shown to be effective in patients with anxiety states without a primary diagnosis of depression. Clinical studies in well-defined patient groups, preferably comparing mirtazapine with an anxiolytic drug, are clearly needed in the future.

Conclusion

In conclusion, mirtazapine at a dosage of 15 to 25 mg/day is more effective than placebo in the treatment of patients with primary anxiety symptoms. It is a well-tolerated treatment, sedation being the only significant adverse event. Combining both antidepressant and anxiolytic properties,

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mirtazapine has a promising future not only in the treatment of depressed patients, but also of non-depressed anxious patients.

Acknowledgements

This study was supported with an educational grant from NV Organon, Oss, The Netherlands. The authors thank Dr W Hamouz, Gelsenkirchen, Germany, for his assistance in the data collection phase of the study.

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