

A DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER STUDY TO ASSESS THE EFFECTS
OF SERTRALINE, ALONE AND WITH DIAZEPAM, ON PSYCHOMOTOR PERFORMANCE

STUDY REPORT: PROTOCOL 206

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SYNOPSIS

PROTOCOL 206 : A DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER STUDY TO ASSESS THE EFFECTS OF SERTRALINE, ALONE AND WITH DIAZEPAM, ON PSYCHOMOTOR PERFORMANCE

Investigator : Dr. I. Hindmarch

A. STUDY DESIGN:

This double-blind placebo-controlled cross-over study in healthy volunteers was designed to compare the effects of 150mg sertraline daily for 7 days with those of placebo on psychomotor performance and on subjective feeling states before and after concurrent administration of 5mg/day diazepam for the last 3 days.

B. SUBJECTS:

	<u>Sertraline</u>	<u>Placebo</u>
Entered Treatment	5	7
Assessed for psychomotor performance	0	0
Assessed for safety	5	7

Psychomotor performance was not assessed because of premature termination of the study.

C. DRUG ADMINISTRATION:

The study was terminated before administration of diazepam to any subject and before the cross-over.

Sertraline was given as 3 x 50mg capsules or 3 x matching placebo once daily for 2-4 days. Diazepam was not administered.

D. RESULTS:

1. Effects on psychomotor performance and subjective feelings: no conclusions could be reached as the study was prematurely terminated.

2. Safety:

No. of subjects with treatment-related:		
side-effects	5/5 (5)	1/7 (1)
abnormal laboratory test results	0/5 (0)	0/7 (0)

() Resulting in discontinuation from treatment.

E. CONCLUSIONS:

This double-blind, placebo-controlled, cross-over study of sertraline in 12 healthy female volunteers was prematurely terminated on day 4 due to complaints of intolerable side-effects by 6 volunteers, 5 of whom were found to be receiving sertraline when the double-blind code was broken. No assessment of psychomotor performance nor of mood was done.

There were no laboratory test abnormalities or clinically significant changes in vital signs related to the study medication. Side-effects in the sertraline group were tremor, insomnia, nausea, asthenia and agitation experienced by all volunteers; dizziness, sweating, dry mouth, and anxiety were reported by four volunteers. Other, less frequent side-effects included headache, somnolence, clammy skin, hypertonia (stiff jaw), vision abnormalities, confusion, vertigo, flushing, mydriasis and rigors (coldness, shivering), none of which required treatment. Some of these side-effects caused concern which may have increased the reporting of symptoms.

One volunteer on placebo reported a variety of mild to moderate side-effects of the same type as the sertraline group.

However, the reason for the high frequency of side-effects in this study remains unknown and this pattern of intolerance to sertraline has not been repeated in other studies.

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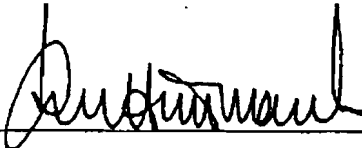
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TITLE OF STUDY: Study Report: Protocol 206

A Double-blind Placebo-Controlled, Crossover Study To Assess The Effects of Sertraline, Alone and with Diazepam, on Psychomotor Performance.

I, Dr Ian Hindmarch, have read the attached report of the clinical study which I have undertaken with oral doses of Sertraline, 25, 50, 75 and 100 mg. I confirm that the report accurately presents the study as undertaken and that I am in full agreement with the conclusions drawn.

Signed



Date

9/11/88

STUDY REPORT

I. PURPOSE OF STUDY

To assess the effects of repeated daily doses of sertraline on psychomotor performance and compare them with those of matched placebo before and after concurrent administration of diazepam.

II. TRIAL DESIGN

This was to be a double-blind placebo-controlled cross-over study of sertraline in 12 healthy volunteers.

Each volunteer was to receive either sertraline 150mg or placebo once daily for 7 days (6 subjects on each treatment) according to a predetermined randomisation together with diazepam 5mg daily for the last 3 days. The subjects were then to receive the alternative regimen for a further 7 days, with diazepam as before for the last 3 days. A battery of psychomotor tests, a sleep evaluation questionnaire and visual analogue scales of patients' feeling states (mood tests) were to be completed during each treatment period and at the end of the study.

Safety data were to include assessments of side-effects, vital signs and laboratory tests.

FLOW CHART OF INTENDED STUDY ASSESSMENTS AND DOSING

ASSESSMENT	DAY-->	SCREENING	PERIOD 1			PERIOD 2		FINAL ASSESSMENT
			1	5(+)	7	8	12(+)	14
CLINICAL EXAMINATION		X						X
DEMOGRAPHY		X						
PSYCHOMOTOR PERFORMANCE		X(*)	X	X	X	X	X	X
MOOD TESTS			X	X	X	X	X	X
VITAL SIGNS		X	X	X	X	X	X	
SIDE-EFFECTS			X	X	X	X	X	X
LABORATORY TESTS		X	X		X		X	
<u>DOSAGE</u>								
DOUBLE-BLIND THERAPY			X----->X			X----->X		
DIAZEPAM				X--->X			X---->X	

KEY

X : Single assessment.

X-->X : Dosing on day marked and those intervening.

(*) : These tests were to be performed to familiarise the subjects with the tests and to minimise learning effect during the trial.

(+) : All assessments were scheduled pre-dose and 2 hours post-dose.

III. SUBJECT SELECTION CRITERIAA. For Inclusion in Study:

1. Healthy volunteers, aged 18 to 50 years.
2. No evidence of concomitant disease based upon medical history and full physical examination, and with clinical laboratory test results within the normal range for that laboratory.
3. Body weight within the range 60-90kg, and within 10% of ideal for age, height and frame size.
4. Subjects not having received any drug therapy within two weeks prior to the study.
5. Written informed consent.

B. For Exclusion from the Study:

1. Females of child-bearing potential, defined as not using reliable contraceptive methods, pregnant or lactating females.
2. Any gastro-intestinal condition possibly affecting absorption of the drug.
3. Evidence of significant haematological, vascular, renal, hepatic, gastro-intestinal or neurological disease, including all forms of epilepsy, or of any other systemic disease.
4. A history of drug or alcohol abuse, drug allergies or history of psychiatric disease including depressive episodes.
5. Subjects having received a trial medication within 3 months of the start of the study, or regularly taking psychotropic drugs.

IV. CLINICAL OBSERVATIONS AND LABORATORY MEASUREMENTSA. Psychometric Tests:

Following selection, volunteers were to be familiarised with the test procedures and apparatus, to minimise learning effects during the study period.

The volunteers were to be transported daily from their homes to the Unit for the period of study and were to be discharged finally only after both physical and psychological assessment.

No alcohol was permitted for the period from 24 hours prior to baseline to the end of the study, and intake of caffeine-containing beverages was to be maintained at the subjects' normal intake. Concomitant therapy was not permitted.

On days 1, 5 and 7 of each week immediately prior to dosing, and 2 hours post-dosing on day 5 of each week, a battery of psychometric tests was to be completed. These comprised Critical Flicker Fusion (CFF), Complex Reaction Time (CRT), Visual Analogue Scales (VAS) of mood (subjective feelings) and mental arithmetic.

Additionally a sleep evaluation questionnaire (SEQ) was to be completed each day. All methods were in accordance with those previously described by Hindmarch (1975) and by Hindmarch and Parrott (1979).

B. Safety:

1) Side-effects:

During the study, subjects were to be asked to complete side-effect questionnaires at the same time points as psychomotor tests were performed. All reported side-effects were to be recorded together with details of time of onset, duration and the investigator's opinion of relationship to treatment. Leading questions were not permitted.

2) Laboratory Safety Tests:

The following laboratory tests were to be measured at screening during the week prior to the study and on days 1, 7 and 14:

Haematology: haemoglobin, haematocrit, red blood cell, white blood cell differential and platelet counts.

Biochemistry: serum sodium, potassium, chloride, urea, creatinine, alkaline phosphatase, gamma GT, AST (SGOT), ALT (SGPT), bilirubin, glucose.

Urine: Pregnancy test at baseline.

3) Other safety parameters

At screening assessment and prior to discharge from the study a physical examination was required. In addition blood pressure and pulse, both erect and supine, were also required at the same times as the psychometric tests.

V. DEVIATIONS FROM THE PROTOCOL

Only female subjects were selected for the study. However, all subjects satisfied the criteria of using reliable contraceptive methods and had a negative pregnancy test prior to the starting of the study.

The study was terminated on day 4 (see section VI); observations thereafter were not undertaken but additional laboratory safety tests, including determination of plasma sertraline concentrations, were undertaken on day 7, together with blood pressure and heart rate measurements. As a result of the premature termination of the study, the data have been treated as from a parallel group design.

One volunteer (No 007) received the study medication in reverse order to the one she was allocated thus resulting in five sertraline-treated and seven placebo-treated volunteers in the first week (Tables 1 and 2).

Plasma sertraline concentrations on Day 7 indicated that subjects 006 and 009 may have received incorrect dosage on one occasion. The samples however, were in poor condition and an error on labelling may have occurred.

Three subjects received therapy during the two weeks prior to and during the study.

Sertraline group:

- 001 - Oral contraceptive
- 005 - Antifungal therapy (not specified)

Placebo group:

- 002 - Oral iron

In addition, two subjects received other therapy whilst in the study:

Sertraline group:

- 010 - Aspirin/codeine (Codis) on one occasion.

Placebo group:

- 006 - Aspirin preparations on more than one occasion.

Eight subjects (001, 004, 007, 008, 009, 010, 011 and 012) weighed less than 60kg, the minimum specified in the inclusion criteria.

Only supine blood pressure was recorded.

VI. TRIAL INCLUSIONS/EXCLUSIONSA. Discontinuing therapy

All volunteers in the sertraline regimen and one volunteer in the placebo regimen discontinued on or before day 4 of the study due to side-effects (Tables 3 and 4). The study was therefore terminated on day 4.

VII. STATISTICAL METHODOLOGY

No statistical analyses have been done.

VIII. BASELINE SUBJECT CHARACTERISTICS

The demographic data of the participating subjects are summarised in Table 5 and the concurrent diseases at baseline in Table 6. There was only one volunteer with "mononeuritis multiplex" (carpal tunnel syndrome).

IX. DRUG ADMINISTRATION

Each subject was to receive, according to a pre-determined randomisation, seven days treatment with sertraline and seven days treatment with placebo. The treatment order was not followed by one subject - see Section V. The medication was administered as three capsules daily (of 50mg sertraline or of placebo) given as a single dose in the morning. Due to the discontinuation of the study no subjects reached day 5 of the study period and therefore none received diazepam, which was to be given on the 5th-7th days of each treatment period. (Table 8). Concomitant therapy was taken by 5 subjects. (Table 7). See also Section V.

X. RESULTSSafety:1. Side-effects

Table 9 displays the incidence and Table 10 the severity of side-effects by organ system.

One placebo subject and all five sertraline treated subjects experienced side-effects.

Side-effects in the sertraline group were tremor, insomnia, nausea, asthenia and agitation (all volunteers), dizziness, sweating, dry mouth, and anxiety (four out of five

volunteers), headache, somnolence, cold clammy skin, hypertonia (stiff jaw) and visual abnormalities (three out of five volunteers). All but one of the sertraline subjects reported side-effects from the first day of dosing. Other side-effects included confusion, vertigo, flushing, mydriasis, and rigors (coldness, shivering).

Twenty six out of 72 (36%) of the side-effect incidences (dizziness(2), headache(3), tremor(2), agitation(3), anxiety(2), insomnia(4), somnolence(3), nausea(4), palpitations(1), rigors(1) and asthenia(1)) were reported as severe, the remainder being of mild to moderate or unspecified severity, none of which required treatment.

One volunteer allocated to placebo reported a variety of mild to moderate side-effects - of the same type as the sertraline group - none of which required treatment, but which led to discontinuation of trial treatment. However, this subject had measurable sertraline plasma levels.

All the side-effects started 3-4 hours after dosing, were maximal 8-12 hours post-dose and were reported by the investigator to have caused the subjects concern.

Plasma sertraline and desmethylsertraline levels, determined 3-5 days after the last study drug administration, did not suggest that the side-effect incidence was associated with abnormally high concentrations of drug. (See also section X.3. - Plasma drug levels).

2. Laboratory test results

There were no abnormal test results possibly related to therapy (category 9) (Table 11). The review of test results was conservative in that abnormalities were ascribed as possibly related to study therapy if there were no positive indications of other causality. The review procedure is detailed in Appendix I, which also lists abnormal values judged not to be related to study drug (categories 1-8).

3. Other safety parameters

- blood pressure, pulse.

There were no clinically relevant changes in pulse rate or supine blood pressure between day 1 and day 7. Mean values were as follows:-

	<u>Sertraline</u>		<u>Placebo</u> ^a	
	<u>Day 1</u>	<u>Day 7</u>	<u>Day 1</u>	<u>Day 7</u>
Systolic BP (mmHg)	107	107	114	113
Diastolic BP (mmHg)	73	71	76	76
Pulse rate (b/minute)	72	70	77	76

^a excluding subject 008 - baseline data only recorded.

- Plasma drug levels

Blood samples were obtained on day 7 of the study and whole blood concentrations of sertraline and its desmethyl metabolite were determined by Huntingdon Research Centre using gas chromatography. Samples arrived in poor condition at the laboratory and were insufficient for repeat assay. The concentrations of plasma sertraline and desmethylsertraline levels determined 3 to 5 days after the last study drug administration ranged between <5ng/ml and 48ng/ml. (Table 12).

Although volunteers #006 and #009 were supposedly on placebo they had detectable plasma levels of sertraline (13 and 19ng/ml respectively) but no metabolite was detected. In addition volunteer #006 discontinued the study dose due to side effects which were similar to the side effects reported by the volunteers on sertraline. No explanation can be offered for these findings. Subjects #010 and 012 had no detectable levels of sertraline but had metabolite present indicating that they had received sertraline.

SUMMARY

This double-blind, placebo-controlled, cross-over study in healthy volunteers was designed to compare the effects of four once daily doses of 150mg sertraline with those of placebo, before and with concurrent administration of 5mg diazepam for a further three days, on psychomotor performance, mood and a sleep assessment questionnaire. Twelve female volunteers entered the study.

Due to intolerable side-effects in 6 subjects (five found to be on sertraline) the study was terminated on day 4 and thus no subjects were assessable for effects on psychomotor performance, mood or sleep.

The most frequently reported side-effects in the sertraline regimen were tremor, insomnia, nausea, asthenia and agitation (all volunteers), dizziness, sweating, dry mouth, and anxiety (4/5 volunteers), headache, somnolence, cold clammy skin, hypertonia (stiff jaw) and vision abnormalities (3/5 volunteers), all of which were reported from the first dosing day. Other side-effects included confusion, vertigo, flushing, mydriasis and rigors (coldness, shivering). Severe side-effects included dizziness, headache, tremor, agitation, anxiety, insomnia, somnolence, nausea, palpitations, rigors and asthenia, amounting to 36% of the total number of symptoms, none of which required treatment. Some side-effects caused concern and may have resulted in over-reporting of symptoms. However, plasma levels of sertraline determined 3 to 5 days after the last study drug administration did not support the possibility of high levels of drug due to relatively low body weight as causative. Therefore the reason for the high frequency of side-effects in this study remains unknown. Most importantly, it is not reflective of the overall side-effect experience with sertraline.

One volunteer in the placebo regimen complained of a variety of side-effects - of similar type to the sertraline group - all of mild to moderate degree, but which necessitated withdrawal from the study.

All side-effects disappeared on discontinuation of treatment.

There were no clinically significant laboratory test abnormalities.

REFERENCES

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TABLE 1
SUBJECT EVALUATION GROUPS

EVALUATION SUBGROUP	NUMBERS OF SUBJECTS	
	SERTRALINE	PLACEDO
ENTERED TREATMENT	5	7
COMPLETED TREATMENT	0	0
COMPLETED STUDY	0	0
PSYCHOMOTOR TESTS	0	0
SAFETY ANALYSES:		
Side Effects	5	7
Laboratory Tests	5	7
Vital Signs	5	7

TABLE 2
ADMINISTRATION SCHEDULE

Subject Number	First Dosing Period	Second Dosing Period
001	Sertraline	Placebo
002	Placebo	Sertraline
003	Sertraline	Placebo
004	Placebo	Sertraline
005	Sertraline	Placebo
006	Placebo	Sertraline
007*	Placebo	Sertraline
008	Placebo	Sertraline
009	Placebo	Sertraline
010	Sertraline	Placebo
011	Placebo	Sertraline
012	Sertraline	Placebo

* Subject 7 was mistakenly given placebo in the first period as displayed in the table.

H.B. The investigator stopped the study before the first period was complete. Therefore the data displayed in all other tables are as for a parallel group study.

TABLE 3
SUMMARY OF SUBJECTS DISCONTINUING STUDY

REASON FOR DISCONTINUATION	NUMBER OF SUBJECTS	
	Sertraline	Placebo
RELATED TO STUDY DRUG		
Safety: Side effects	5	1
NOT RELATED TO STUDY DRUG		
Other (*)	0	6

(*) Investigator stopped the trial due to the high incidence of side effects

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TABLE 4
REASONS FOR DISCONTINUING TREATMENT - SUBJECT LISTING

SUBJECT NUMBER	SEX	AGE (YRS)	DOSE AT TIME OF WITHDRAWAL (mg/day)	DURATION OF TREATMENT (days)	REASONS FOR DISCONTINUATION
SERTRALINE					
001	F	35	150	3	Side effects: agitation, anxiety, insomnia, dizziness, headache, tremor, vision abnormal, anorexia, diarrhoea, nausea, asthenia, rigors
003	F	27	150	4	Side effects: agitation, insomnia, dystonia, headache, tremor, sweating increased, mouth dry, vision abnormal, dysphagia, nausea, asthenia
005	F	35	150	3	Side effects: agitation, anxiety, insomnia, somnolence, dizziness, tremor, sweating increased, flushing, mouth dry, skin cold clammy, anorexia, nausea, palpitations, asthenia, rigors
010	F	36	150	3	Side effects: agitation, anxiety, insomnia, somnolence, dystonia, confusion, dizziness, headache, tremor, sweating increased, flushing, mouth dry, mydriasis, skin cold clammy, vision abnormal, dysphagia, nausea, tooth disorder, palpitations, asthenia, malaise
012	F	37	150	2	Side effects: agitation, anxiety, insomnia, somnolence, dystonia, dizziness, tremor, sweating increased, mouth dry, skin cold clammy, eye pain, nausea, asthenia
PLACEBO					
002	F	33	0	4	Investigator terminated the study
004	F	34	0	4	Investigator terminated the study
006	F	40	0	3	Side effects: aggressive reaction, agitation, anxiety, insomnia, somnolence, coordination abnormal, dizziness, headache, tremor, nausea, asthenia, fatigue, malaise
007	F	36	0	4	Investigator terminated the study
008	F	35	0	4	Investigator terminated the study
009	F	41	0	4	Investigator terminated the study
011	F	37	0	4	Investigator terminated the study

NOTE : Some of the side effects listed may have disappeared before the study was terminated. However it was their presence in such large numbers at some stage during the study which caused the investigator to stop the study. Thus all side effects have been listed for all subjects.

TABLE 5
SUBJECT AGE AND WEIGHT

	Sertraline	Placebo
	Female	Female
No. of Subjects	5	7
Age Category		
<15	0	0
15-24	0	0
25-34	1	2
35-44	4	5
>44	0	0
Mean Age (yrs)	34.0	36.9
Age Range	27- 37	33- 43
Mean Weight (kg)	56.3	56.8
Weight Range	47- 65	45- 70

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TABLE 6

CONCURRENT DISEASES AT BASELINE

Disease	Sertraline	Placebo
Mononeuritis of upper limb/mononeuritis multiplex	1	0
Number of subjects with at least one concurrent disease	1	0

TABLE 7
 CONCOMITANT THERAPY DURING DOUBLE-BLIND TREATMENT

THERAPY	NUMBER OF SUBJECTS	
	Sertraline	Placebo
CONTRACEPTIVES	1	0
DRUGS USED IN ANEMIAS	0	1
DRUGS USED IN RHEUMATIC DISEASES AND GOUT	1	1
ANTI-INFECTION SKIN PREPARATIONS	1	0
NUMBER OF SUBJECTS WITH AT LEAST ONE CONCURRENT THERAPY	3	2

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TABLE 8
TOTAL DURATION OF DOUBLE-BLIND TREATMENT (days)

	Treatment Group	
	Sertraline	Placebo
Number of Subjects	5	7
Duration (days)		
<4	4	1
4-10	1	6
>10	0	0
Mean Duration	3.0	3.9
Range (Days)	2 - 4	3 - 4

TABLE 9
INCIDENCE OF SIDE EFFECTS DURING DOUBLE-BLIND TREATMENT

	Sertraline	Double Blind Placebo
NUMBER OF SUBJECTS:		
Evaluable	5	7
With Side Effects	5	1
Withdrawn with Side Effects	5	1
SIDE EFFECTS BY ORGAN SYSTEM		
NUMBER OF SUBJECTS WITH:		
Psychiatric Disorders	5	1
Centr & Periph Nerv Syst Disorders	5	1
Autonomic Nervous System Disorders	4	0
Special Senses Disorders	4	0
Gastro-Intestinal Disorders	5	1
Cardiovascular Disorders	2	0
Body as a Whole - General Disorders	5	1

Information on relationship to study drug was not recorded.

TABLE 10
SEVERITY OF SIDE EFFECTS DURING DOUBLE-BLIND TREATMENT

ORGAN SYSTEM Side Effect	Sertraline					Double Blind Placebo				
	Number of Subjects	1	2	3	NS	Number of Subjects	1	2	3	NS
Psychiatric Disorders										
Aggressive Reaction	0	0	0	0	0	1	1	0	0	0
Agitation	5	2	0	3	0	1	1	0	0	0
Anxiety	4	1	1	2	0	1	1	0	0	0
Insomnia	5	0	1	4	0	1	0	1	0	0
Somnolence	3	0	0	3	0	1	0	1	0	0
Centr & Periph Nerv Syst Disorders										
Confusion	1	0	0	0	1	0	0	0	0	0
Coordination Abnormal	0	0	0	0	0	1	0	0	0	1
Dizziness	4	0	2	2	0	1	1	0	0	0
Headache	3	0	0	3	0	1	0	1	0	0
Hypertonia	3	0	0	0	3	0	0	0	0	0
Tremor	5	2	1	2	0	1	1	0	0	0
Autonomic Nervous System Disorders										
Sweating Increased	4	2	2	0	0	0	0	0	0	0
Flushing	2	0	2	0	0	0	0	0	0	0
Mouth Dry	4	2	2	0	0	0	0	0	0	0
Hydrasis	1	0	0	0	1	0	0	0	0	0
Skin Cold Clammy	3	1	0	0	2	0	0	0	0	0
Special Senses Disorders										
Eye Pain	1	0	0	0	1	0	0	0	0	0
Vision Abnormal	3	2	1	0	0	0	0	0	0	0

SEVERITY CODES : 1 = MILD 2 = MODERATE 3 = SEVERE NS = NOT SPECIFIED

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TABLE 10 (continued)
SEVERITY OF SIDE EFFECTS DURING DOUBLE-BLIND TREATMENT

ORGAN SYSTEM Side Effect	Sertraline					Double Blind Placebo				
	Number of Subjects	1	2	3	NS	Number of Subjects	1	2	3	NS
Gastro-Intestinal										
Anorexia	2	0	0	0	2	0	0	0	0	0
Diarrhoea	1	0	0	0	1	0	0	0	0	0
Dysphagia	2	0	0	0	2	0	0	0	0	0
Nausea	5	1	0	4	0	1	0	1	0	0
Tooth Disorder	1	0	0	0	1	0	0	0	0	0
Cardiovascular Disorders										
Palpitations	2	0	1	1	0	0	0	0	0	0
Body as a Whole - General Disorders										
Asthenia	5	3	1	1	0	1	1	0	0	0
Fatigue	0	0	0	0	0	1	0	0	0	1
Malaise	1	0	0	0	1	1	0	0	0	1
Rigors	2	0	1	1	0	0	0	0	0	0
Totals (*)	72	16	15	26	15	13	6	4	0	3

SEVERITY CODES : 1 = MILD 2 = MODERATE 3 = SEVERE NS = NOT SPECIFIED
(*) The numbers in this row are the total numbers of side effects and not the numbers of subjects with side effects.

TABLE 11
LABORATORY TEST ABNORMALITIES - MAY BE RELATED TO TREATMENT

LABORATORY TEST	SUBJECT NUMBER	UNITS	NORMAL LIMITS	BASELINE VALUE	MOST DIVERGENT VALUE
Sertraline					
No drug-related abnormalities					
Double Blind Placebo					
No drug-related abnormalities					

TABLE 12

Concentrations of Sertraline and Desmethylsertraline in whole blood samples from subjects receiving Sertraline, 150mg daily

Results are expressed as ng/ml

Patient No.	Concentration of Sertraline	Concentration of Desmethylsertraline
1	33	84
2	ND	ND
3	11	20
4	ND	ND
5	48	110
6	13	ND
7	ND	ND
9	18	ND
10	ND	31
11	ND	ND
12	ND	39

ND = Not detected < 5ng/ml

No data available for volunteer 008 (insufficient sample)

It can be seen that volunteers 006 and 009 although on placebo had detectable plasma levels of sertraline but of no metabolite. No explanation can be offered for these findings. Subjects 010 and 012 had no detectable sertraline, but had metabolite present.

APPENDIX I

Page No.

SUPPLEMENTAL ADVERSE EVENT DATA

TABLE 1	INCIDENCE OF SIDE-EFFECTS (ALL CAUSALITIES) DURING DOUBLE-BLIND TREATMENT	1145
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APPENDIX I SUPPLEMENTAL ADVERSE EVENT DATA FOR PROTOCOL 206 (HINDMARCH)

TABLE 1 INCIDENCE OF SIDE EFFECTS (ALL CAUSALITIES) DURING DOUBLE-BLIND TREATMENT

	Sertraline	Double Blind Placebo
NUMBER OF SUBJECTS:		
Evaluable	5	7
With Side Effects	5	1
Withdrawn with Side Effects	5	1
SIDE EFFECTS BY ORGAN SYSTEM		
NUMBER OF SUBJECTS WITH:		
Psychiatric Disorders	5	1
Centr & Periph Nerv Syst Disorders	5	1
Autonomic Nervous System Disorders	4	0
Special Senses Disorders	4	0
Gastro-Intestinal Disorders	5	1
Cardiovascular Disorders	2	0
Body as a Whole - General Disorders	5	1

APPENDIX I SUPPLEMENTAL ADVERSE EVENT DATA FOR PROTOCOL 206 (HINDMARCH)

TABLE 2 SEVERITY OF SIDE EFFECTS (ALL CAUSALITIES) DURING DOUBLE-BLIND TREATMENT

ORGAN SYSTEM Side Effect	Sertraline					Double Blind Placebo				
	Number of Subjects	1	2	3	NS	Number of Subjects	1	2	3	NS
Psychiatric Disorders										
Aggressive Reaction	0	0	0	0	0	1	1	0	0	0
Agitation	5	2	0	3	0	1	1	0	0	0
Anxiety	4	1	1	2	0	1	1	0	0	0
Insomnia	5	0	1	4	0	1	0	1	0	0
Somnolence	3	0	0	3	0	1	0	1	0	0
Centr & Periph Nerv Syst Disorders										
Confusion	1	0	0	0	1	0	0	0	0	0
Coordination Abnormal	0	0	0	0	0	1	0	0	0	1
Dizziness	4	0	2	2	0	1	1	0	0	0
Headache	3	0	0	3	0	1	0	1	0	0
Hypertonia	3	0	0	0	3	0	0	0	0	0
Tremor	5	2	1	2	0	1	1	0	0	0
Autonomic Nervous System Disorders										
Sweating Increased	4	2	2	0	0	0	0	0	0	0
Flushing	2	0	2	0	0	0	0	0	0	0
Mouth Dry	4	2	2	0	0	0	0	0	0	0
Mydriasis	1	0	0	0	1	0	0	0	0	0
Skin Cold Clammy	3	1	0	0	2	0	0	0	0	0
Special Senses Disorders										
Eye Pain	1	0	0	0	1	0	0	0	0	0
Vision Abnormal	3	2	1	0	0	0	0	0	0	0

SEVERITY CODES : 1 = MILD 2 = MODERATE 3 = SEVERE NS = NOT SPECIFIED

Z0000176

1146

APPENDIX I SUPPLEMENTAL ADVERSE EVENT DATA FOR PROTOCOL 206 (HINDMARCH)

TABLE 2 SEVERITY OF SIDE EFFECTS (ALL CAUSALITIES) DURING DOUBLE-BLIND TREATMENT

ORGAN SYSTEM Side Effect	Sertraline					Double Blind Placebo				
	Number of Subjects	1	2	3	NS	Number of Subjects	1	2	3	NS
Gastro-Intestinal										
Anorexia	2	0	0	0	2	0	0	0	0	0
Diarrhoea	1	0	0	0	1	0	0	0	0	0
Dysphagia	2	0	0	0	2	0	0	0	0	0
Nausea	5	1	0	4	0	1	0	1	0	0
Tooth Disorder	1	0	0	0	1	0	0	0	0	0
Cardiovascular Disorders										
Palpitations	2	0	1	1	0	0	0	0	0	0
Body as a Whole - General Disorders										
Asthenia	5	3	1	1	0	1	1	0	0	0
Fatigue	0	0	0	0	0	1	0	0	0	1
Malaise	1	0	0	0	1	1	0	0	0	1
Rigors	2	0	1	1	0	0	0	0	0	0
Totals (**)	72	16	15	26	15	13	6	4	0	3

SEVERITY CODES : 1 = MILD 2 = MODERATE 3 = SEVERE NS = NOT SPECIFIED

(**) The numbers in this row are the total numbers of side effects and not the numbers of subjects with side effects.

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1147

LABORATORY TEST RESULTS OUTSIDE NORMAL RANGE CONSIDERED NOT RELATED TO DRUG

All laboratory test data for each subject were reviewed. For each parameter where results deviated from the normal range, the most abnormal value was recorded and the pattern of abnormal values categorized. Each pattern of abnormal values was considered potentially related to drug therapy unless it fell into one of the following categories.

List 1 defines abnormalities when the baseline value was normal or was missing. List 2 defines changes when the baseline was abnormal.

- Category N The baseline value was normal, abnormal or missing and all values during therapy were within the normal range. This category ensures that all patients are accounted for.
- Category 1 The baseline value was outside the normal range and the deviation of the most abnormal value from baseline during therapy was so small as to be clinically insignificant.
- Category 2 The baseline value was normal or missing and the deviation of the most abnormal value from normal during therapy was so small as to be clinically insignificant.
- Category 3 The baseline value was normal or missing and there was a single, significant abnormal value which returned to normal during therapy.
- The baseline value was outside the normal range and there was a single divergent value that differed significantly from baseline, but returned to within these limits during therapy.
- Category 4 The baseline value was normal or missing and there were two or three significant abnormal values within a six (6) week period that all lie on the same side of the normal range; no value reached the level of marked abnormality and the last two values during therapy were within normal limits. The abnormal values were consecutive or were interspersed with normal values.

The baseline value was outside the normal range and there were two or more significant abnormal values compared to baseline within a six (6) week period and all lie on the same side of the normal range as the baseline; the values did not differ significantly from baseline for the last two values during therapy. The abnormal values were consecutive, or there were abnormal values differing significantly from baseline, interspersed with values differing less than the insignificant percent from baseline.

Category 5 There was a documented laboratory error.

Category 6 The abnormality appeared likely to be due to the primary disease or to a coexisting disease process.

Category 7 The abnormality appeared likely to be due to concomitant drug therapy.

Category 8 The abnormality was considered to be clinically insignificant or not due to therapy upon review by a physician.

Abnormalities which were considered to be potentially related to drug therapy were assigned to Category 9 and may be found in the body of this study summary.

The abnormalities not related to drug are recorded in Table 3.

* See List 2
** See List 1

LIST 1

DEFINITION OF ABNORMAL TEST VALUES WHEN BASELINE VALUE WAS NORMAL OR MISSING

LABORATORY TEST	CLINICALLY RELEVANT DIRECTION ^a	ABNORMALITY	MARKED ABNORMALITY
HGB	Decrease	10%	25%
HCT	Decrease	10	25
RBC	Either	10	25
PLATELETS	Decrease	10	25
WBC	Either	10	25
NEUTROS (ABS)	Either	10	25
EOS (ABS)	Increase	25	50
BASOS (ABS)	Increase	25	50
LYMPHS (ABS)	Either	10	25
MONOS (ABS)	Increase	25	50
BANDS (ABS)	Increase	10	25
TOTAL BILIRUBIN	Increase	10	50
DIRECT BILIRUBIN	Increase	10	50
INDIRECT BILIRUBIN	Increase	10	50
TOTAL PROTEIN	Either	5	25
SERUM ALBUMIN	Either	5	25
SERUM GLOBULIN	Either	10	50
SGOT	Increase	10	50
CPK	Increase	10	50
SGPT	Increase	10	50
GGT	Increase	10	50
LDH	Increase	10	50
ALKALINE PHOSPHATASE	Increase	10	50
BLOOD UREA	Increase	10	50
BUN	Increase	10	50
CREATININE	Increase	10	50
URIC ACID	Increase	10	50
SODIUM	Either	5	25
POTASSIUM	Either	5	25
CHLORIDE	Either	5	25
CO2	Either	5	25
CALCIUM	Either	5	25
INORGANIC PHOSPHORUS	Either	5	25
GLUCOSE, FASTING	Either	10	50
GLUCOSE, RANDOM	Either	10	50

^a Only clinically relevant direction of abnormality considered and percent limits applied to the limit on normal range closest to that abnormality.

DEFINITION OF ABNORMAL TEST VALUES WHEN BASELINE VALUE WAS ABNORMAL

LABORATORY TEST	CLINICALLY RELEVANT DIRECTION ^a	ABNORMALITY	MARKED ABNORMALITY
HGB	Decrease	5%	10%
HCT	Decrease	5	10
RBC	Either	5	10
PLATELETS	Decrease	10	25
WBC	Either	20	50
NEUTROS (ABS)	Either	10	25
EOS (ABS)	Increase	25	50
BASOS (ABS)	Increase	25	50
LYMPHS (ABS)	Either	10	25
MONOS (ABS)	Increase	25	50
BANDS (ABS)	Increase	10	25
TOTAL BILIRUBIN	Increase	10	50
DIRECT BILIRUBIN	Increase	10	50
INDIRECT BILIRUBIN	Increase	10	50
TOTAL PROTEIN	Either	5	25
SERUM ALBUMIN	Either	5	25
SERUM GLOBULIN	Either	10	50
SGOT	Increase	20	50
CPK	Increase	20	50
SGPT	Increase	20	50
GGT	Increase	20	50
LDH	Increase	20	50
ALKALINE PHOSPHATASE	Increase	20	50
BLOOD UREA	Increase	10	50
BUN	Increase	10	50
CREATININE	Increase	10	50
URIC ACID	Increase	10	50
SODIUM	Either	5	25
POTASSIUM	Either	5	25
CHLORIDE	Either	5	25
CO2	Either	5	25
CALCIUM	Either	5	25
INORGANIC PHOSPHORUS	Either	5	25
GLUCOSE, FASTING	Either	20	50
GLUCOSE, RANDOM	Either	20	50

^a Only clinically relevant direction of abnormality considered and percent limits applied to the change from abnormal baseline.

APPENDIX I SUPPLEMENTAL ADVERSE EVENT DATA FOR PROTOCOL 106 (HINDMARCH)

TABLE J LABORATORY TEST RESULTS OUTSIDE NORMAL RANGE CONSIDERED NOT RELATED TO TREATMENT

SERIALINE TREATMENT GROUP						
LABORATORY TEST	SUBJECT ID	NORMAL RANGE	UNITS	BASELINE VALUE	MOST DIVERGENT VALUE	CATEGORY
No laboratory abnormalities						
DOUBLE BLIND PLACEBO TREATMENT GROUP						
LABORATORY TEST	SUBJECT ID	NORMAL RANGE	UNITS	BASELINE VALUE	MOST DIVERGENT VALUE	CATEGORY
Haematocrit	002	37-47	%	36.1	36.3	1
	006	37-47	%	36.2	33.8	4
Red Blood Cells	006	3.9-5.6	10 ¹² /L	4.11	3.82	2
WBC	006	4-11	10 ⁹ /L	5.9	3.3	8

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