9. QUESTION 9

Provide a review of the benefit-risk balance of paroxetine in the elderly (>65 years of age) particularly in relation to its anti-cholinergic effects, co-morbidity and polypharmacy.

Response

9.1. Introduction

Paroxetine has been used extensively by elderly patients since it was introduced in the early 1990's. It has been well studied in this population as was reflected in a recent review [Wagstaff, 2002]. Increased plasma concentrations of paroxetine occur in elderly subjects, as they do in subjects with severe renal and hepatic impairment. For that reason dosing in the elderly is limited to a maximum of 40mg daily.

9.2. Efficacy of paroxetine in the elderly

9.2.1. Placebo-controlled studies in depression

A 12 week trial, Study 487, conducted in 1996-1997, was the largest placebo-controlled study of paroxetine specifically in the elderly. It enrolled elderly outpatients (≥60 years of age) with depression and employed a three-arm placebo-controlled, flexible dose design which included controlled release (CR) as well as immediate release (IR) paroxetine.

In study 487, patients on active medication began treatment at 10 mg/day paroxetine IR or 12.5 mg/day paroxetine CR (Dosage Level 1) for one week, and thereafter the Dosage Level was titrated upward no more frequently than one Level (10mg increments) per week according to the patient's therapeutic response and tolerability. The maximum Dosage Level permitted was Level 4, i.e., paroxetine IR 40 mg/day or paroxetine CR 50 mg/day.

Male and female outpatients who met the Diagnostic and Statistics Manual of Mental Disorders criteria for Major Depressive Disorder (DSM-IV 296.2 or 296.3) at a screening visit were entered into study 487. Patients with a primary diagnosis of other psychiatric disorders, such as Panic Disorder, Obsessive Compulsive Disorder, Social Phobia, Dysthymia, bipolar affective disorder, and schizophrenia were excluded, as were patients with a recent histories of substance dependence or abuse. Patients who required ongoing treatment with concomitant psychotropic medications were also excluded from participating, as were those with serious uncontrolled medical disorders.

At the screening visit, patients had to have a Hamilton Depression Rating scale (HAMD, 17-item) total score of 18 or more. Eligible patients then underwent a seven day, single-blind placebo run-in period during which the HAMD total score could not have decreased by more than 25% from the score obtained at screening.

A total of 319 outpatients made up the ITT population in study 487, which included 106 patients treated with paroxetine IR, 104 with paroxetine CR and 109 with placebo.

Demographic characteristics in the ITT population were similar between the paroxetine IR and CR groups and the placebo group, (Table 9.1). In addition, other characteristics were similar between groups, including medical and psychiatric history and prior and concomitant use of psychotropic and non-psychotropic medications.

Table 9.1 Summary of Demographic Data Study 487 - ITT Population

		Age (years)			Gender [n (%)]		Race [n (%)]	
Treatment	N	Mean	S. D.	Range	Female	Male	White	Nonwhite
Paroxetine IR	106	70.05	6.59	60-88	60 (57)	46 (43)	101 (95)	5 (5)
Paroxetine CR	104	70.39	5.93	60-88	50 (48)	54 (52)	100 (96)	4 (4)
Placebo	109	69.39	5.40	60-82	69 (63)	40 (37)	103 (94)	6 (6)

In the paroxetine IR and CR groups and the placebo group of study 487, mean baseline HAMD Total score was 22, and the mean (median) duration of the present episode of depression was 3.4 (1.4), 2.9 (1.2), and 4.1 (1.7) years, respectively. The mean (median) time since the first onset of depressive illness was 15.1 (7.0), 17.2 (6.7), and 13.6 (8.0) years, respectively. No more than 5% of patients in all 3 treatment groups combined in study 487 reported a particular comorbid psychiatric illness that had been diagnosed previously.

The number and reasons for patient withdrawals after randomization to double-blind treatment in study 487 are presented in Table 9.2. Over 70% of patients completed 12 weeks of treatment in all three treatment groups in this study.

Table 9.2 Patient Disposition Study 487 - ITT Population

Treatment Group	Number Randomized		Completed Week 12		Withdrawn due to Adverse Event		Withdrawn due to Lack of Efficacy		Withdrawn due to Protocol Deviation		Lost to Followup		Other Reasons	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Paroxetine IR	106	100	76	71.7	17	16.0	2	1.9	8	7.5	1	0.9	2	1.9
Paroxetine CR	104	100	81	77.9	13	12.5	4	3.8	3	2.9	1	1.0	2	1.9
Placebo	109	100	84	77.1	9	8.3	5	4.6	3	2.8	3	2.8	5	4.6

The primary conclusions concerning the efficacy of paroxetine were made using the Week 12 Endpoint, i.e., the last observation carried forward dataset (LOCF) at Week 12 of the Intention-to-Treat population. Results obtained at Week 12 LOCF were generally confirmed for all efficacy variables by results obtained for patients who completed 12 weeks of treatment (Week 12 Observed Cases dataset). The change from baseline to study endpoint in the total score of the 17 item investigator-rated Hamilton Depression Rating scale (HAMD) was the primary efficacy variable used to assess antidepressant efficacy.

The analysis of the primary efficacy variable from study 487 is presented in Table 9.3. There was a -12.3 mean change from baseline in HAMD total score at the Week 12 Endpoint for the paroxetine IR group, and the mean difference in this response versus placebo (-2.8) was statistically significant (p=0.003). These effects of paroxetine IR in an elderly population are considered to be clinically relevant and are at least as large as effects obtained in a study with a very similar design (but using 20 – 50 mg/day paroxetine IR) in a general "adult" patient population (Study 449, mean difference versus placebo –1.9).

Table 9.3 HAMD Total Score - Mean Change From Baseline Study 487 – ITT Population Week 12 Endpoint

Study	N	Mean Baseline HAMD total score (s.e.)	Mean Change at Endpoint (s.e.)[a]	Diff.	95% Conf. Interval Active – Placebo	p-value Active – Placebo
Paroxetine IR	103	22.3 (0.31)	-12.3 (0.70)	-2.8	-4.65,-0.99	0.003
Paroxetine CR	103	22.1 (0.34)	-12.1 (0.73)	-2.6	-4.47,-0.73	0.007
Placebo	107	22.1 (0.29)	-9.5 (0.71)			

[a]Results are from model that adjusts for centre and covariates.

The results of analyses of secondary efficacy variables also provided evidence of the efficacy of paroxetine in the elderly.

The analysis of mean changes from baseline in the HAMD depressed mood item at Week 12 Endpoint is presented in Table 9.4. The mean difference in the paroxetine IR (and CR) change versus placebo was statistically significant.

Table 9.4 HAMD Depressed Mood Item - Mean Change From Baseline Study 487 – ITT Population Week 12 Endpoint

Regimen	N	Baseline HAMD Depressed Mood Item Score		Change at Endpoint		Diff.	95% Conf. Interval Active vs Placebo	p-value Active vs Placebo
		Mean	(s.e)	Mean	(s.e)			
Paroxetine IR	103	2.8	(0.06)	-1.4	(0.15)	-0.5	-0.83,-0.26	<0.001
Paroxetine CR	103	2.7	(0.06)	-1.4	(0.15)	-0.5	-0.81,-0.22	<0.001
Placebo	107	2.7	(0.06)	-0.9	(0.15)			

For the CGI severity of illness item in study 487 (Table 9.5), there also was a statistically significant difference in the distribution of change from baseline scores for paroxetine IR (and CR) compared to placebo at Week 12 Endpoint.

Table 9.5 Distribution of CGI Severity of Illness Item Change From Baseline Study 487 – ITT Population Week 12 Endpoint

Change from Baseline	Paroxetine IR N=103		Paroxetine CR N=103		Placebo N=106		p-value	
	n	%	n	%	n	%	IR /PL	CR/ PL
-5	1	1.0	3	2.9	2	1.9	0.019	0.022
-4	4	3.9	5	4.9	3	2.8		
-3	25	24.3	17	16.5	12	11.3		
-2	25	24.3	32	31.1	22	20.8		
-1	23	22.3	22	21.4	31	29.2		
0	24	23.3	20	19.4	36	34.0		
1	1	1.0	3	2.9	0	0.0		
2	0	0.0	1	1.0	0	0.0		

Treatment of the elderly population in study 487 with paroxetine IR (and CR) revealed a significantly greater proportion of patients who achieved a HAMD total score ≤ 8 relative to placebo at Week 12 Endpoint (Table 9.6).

Table 9.6 Percentage of Patients with a Therapeutic Response Study 487 – ITT Population Week 12 Endpoint

Regimen	% of Patients	Odds Ratio	95% CI Active – Placebo	p value Active – Placebo
HAMD Total Score ≤ 8 at Study Endpoint				
Paroxetine IR	53.4	2.56	1.43,4.59	0.002
Paroxetine CR	49.0	2.22	1.23,4.01	0.008
Placebo	31.8			

Study 487 clearly demonstrated the effectiveness of paroxetine in the treatment of major depression in elderly patients. The principle evidence of efficacy is based on statistically significant differences from placebo in the mean change from baseline in the Hamilton Depression Rating scale total score and the HAM-D depressed mood item score at Week 12 Endpoint. Similarly, the responder analysis indicates that a statistically and clinically relevant greater percentage of elderly patients achieve remission, defined by a HAM-D total score of ≤8 at the Week 12 Endpoint.

A meta-analyses of placebo-controlled studies presented in the original MAA for paroxetine further supports the efficacy of paroxetine in the treatment of the elderly. It was based on placebo-controlled studies conducted worldwide and compared the HAMD and CGI variables for the population aged <65 (n=1395 paroxetine vs n=518 placebo) with those aged ≥65 (n=248, paroxetine vs n=21 placebo). A significant treatment effect was seen in favour of paroxetine regarding mean change from baseline in HAM-D: (-11.3 paroxetine vs -8.9 placebo for patients <65, and -10.7 paroxetine vs -8.9 placebo for patients ≥65 years, p=0.002) with no significant age effect (p=0.451) or significant treatment by age interaction (p=0.176). Mean change in CGI severity of illness scores were also significantly superior for paroxetine compared to placebo (-1.3 paroxetine vs -0.7 placebo for patients < 65 years; -1.5 paroxetine vs -0.9 placebo for patients ≥65 years, p=0.0001). Again, there were no significant age (p=0.173) or treatment by age interactions (p=0.711). These results indicate that paroxetine was similarly effective in the treatment of depressed patients whether they were older or younger than 65 years.

9.2.2. Active control studies in Depression

The original MAA (Nov 1989) also presented data from four double-blind, active comparator studies conducted in 431 elderly patients (217 received paroxetine 10-40mg/day) with depression (Studies 006, 011, 290 and 291). Patients were all aged ≥60 years and most aged ≥65 years (74%). Paroxetine (10-40mg) was compared to doxepin (50-200mg) in two studies. The other two studies were both fixed dose comparisons of paroxetine and clomipramine. In one study 30mg paroxetine was compared to 75mg clomipramine. In the other 20mg paroxetine was compared to 60mg clomipramine. There were no significant differences between treatment groups in terms of baseline characteristics. Mean baseline HAM-D total scores indicated that patients had moderate to severe depression at entry to these studies. The primary efficacy variables were based on change from baseline in total HAM-D scores for 3 of the studies and the MADRS was used in the final study (291). All treatments showed improvements in depressive

symptomatology. Paroxetine and the active comparators studied demonstrated similar efficacy. However, these studies were not specifically powered to detect equivalence and assay sensitivity was not confirmed as comparison to placebo was not included in those studies.

Another meta-analysis explored the influence of increasing age from 60 years upwards. Ten double-blind, comparative studies in elderly patients were included in the analysis (paroxetine [n=387] and active controls [amitriptyline n=110; clomipramine n=109; doxepin n=102; mianserin n=28]). All studies were of 5-6 weeks duration. Paroxetine (20-30mg) demonstrated a significantly better response than active controls at Weeks 5 to 6 of therapy. The mean change in HAM-D from baseline for paroxetine and the active control group were –15.3 and –13.5, respectively at week 5/6 ($p<0.05$). An advantage for paroxetine was also seen when the HAM-D responder rate (≧50% reduction from baseline) was considered [Dunbar, 1995].

A double-blind, active controlled study of paroxetine (20 to 40mg) versus fluoxetine (20 to 60mg), Study 061, has also been conducted in 106 depressed elderly patients (≥65 years). Patients groups were well matched in terms of baseline psychiatric and demographic characteristics. Mean HAM-D total scores indicated that the patients had moderate MDD. There were no significant differences between treatments at the end of the 6 week study, although there was a statistically significant difference ($p<0.05$) between treatments in mean change from baseline of HAM-D total score at week 3 in favour of paroxetine. Results obtained using the Mini-Mental State Examination (MMSE) and Sandoz Clinical Assessment Geriatric Scale (SCAG) showed that, during treatment, patients in the paroxetine group were characterised by greater improvement in cognitive function than were those in the fluoxetine group. This finding was statistically significant at week 3 for both scales ($p<0.05$) [Schone, 1993].

9.2.3. Additional efficacy analysis in Depression and GAD

Question 9 has asked particularly about the benefit-risk balance of paroxetine in the elderly (>65 years of age) in relation to its anti-cholinergic effects, co-morbidity and polypharmacy. The early studies conducted with paroxetine did not record information on other illnesses and concomitant medication as rigorously as more recent studies. Hence to be confident of providing meaningful information in our response, analyses have been restricted to elderly patients aged >65 years enrolled in studies for which full information on concomitant medication and illnesses is available and which enrolled at least 10 patients aged > 65 years to paroxetine and placebo treatment. Data from those studies have been pooled to provide the safety assessment requested. Those studies (Studies 487, 625, 637, 646) were not all of patients with the same indication. Two were in patients with depression (487, 625), and two with generalised anxiety disorder (GAD).

Efficacy in the population of patients aged >65 years in these studies was therefore assessed by analysing proportion of responders as defined by CGI Global Improvement scores of 1 (very much improved) or 2 (much improved) at endpoint, as CGI Global Improvement was measured in all four studies. In this population, significantly more patients aged >65 years responded to paroxetine than to placebo (paroxetine 59.4%

(221/372), placebo 45.5% (122/268), odds ratio 1.75, 95% CI [1.28, 2.41], p<0.001), (Data Source: Appendix 1, Table 1.38).

9.3. Tolerability of paroxetine in the elderly (>65 years)

As in the general population, in elderly patients SSRIs are generally better tolerated than TCAs. Data from randomised double-blind trials in patients aged ≥60 years with major depressive disorder suggest that paroxetine 10 to 40 mg/day is associated with a lower incidence of adverse events than amitriptyline 50 to 150 mg/day [Hutchinson, 1992] [Geretsegger, 1995], nortriptyline 20 to 125 mg/day [Bump, 2001], clomipramine 25 to 75 mg/day [Guillibert, 1989] and doxepin up to 200 mg/day [Dunner, 1992]. In particular the TCAs were associated with a higher incidence of anticholinergic adverse events (dry mouth, somnolence, constipation); comparative incidences were 7% for paroxetine versus 25% for amitriptyline (p=0.04) [Hutchinson, 1992] and 18% versus 41% for clomipramine (p=0.021) [Guillibert, 1989].

Similar incidences of adverse events in the elderly were noted when paroxetine 20 to 40 mg/day was compared with fluoxetine 20 to 60 mg/day [Schone, 1993]. Commonly occurring adverse events in both groups included somnolence, nausea, diarrhoea, headache, anxiety, sweating and insomnia. There was a trend towards a higher incidence of vomiting with paroxetine (14.8% vs 7.7% for fluoxetine); the incidences of diarrhoea (1.9% vs 11.5%) and sweating (1.9% vs 9.6%), however, were both higher with fluoxetine [Schone, 1993].

Adverse events reported from patients aged >65 years in studies 487, 625, 637 and 646 are shown in Table 9.7, (Data Source: Appendix 1, Table 1.39).

Table 9.7 Number (%) of Patients with Adverse Events on Therapy by Preferred Term and by Descending Order of Paroxetine Frequency in the Elderly (>65 years), (greater than or equal to 2.5% on paroxetine)
Adult Placebo Controlled Trials (Studies 487, 625, 637, 646)
Randomised Phase

Preferred Term	**Paroxetine** N = 406 **n (%)**	**Placebo** N =282 **n (%)**
Total number of patients with AEs	**286 (70.4)**	**174 (61.7)**
Somnolence	59 (14.5)	15 (5.3)
Nausea	48 (11.8)	25 (8.9)
Asthenia	48 (11.8)	15 (5.3)
Headache	47 (11.6)	30 (10.6)
Diarrhoea	47 (11.6)	15 (5.3)
Constipation	45 (11.1)	8 (2.8)
Dry Mouth	40 (9.9)	19 (6.7)
Insomnia	39 (9.6)	24 (8.5)
Dizziness	35 (8.6)	17 (6.0)
Impotence*	15 (8.0)	3 (2.8)
Tremor	30 (7.4)	2 (0.7)
Respiratory Disorder	27 (6.7)	21 (7.4)
Decreased Appetite	26 (6.4)	3 (1.1)
Sweating	25 (6.2)	5 (1.8)
Dyspepsia	24 (5.9)	11 (3.9)
Flatulence	20 (4.9)	10 (3.5)
Abnormal Ejaculation*	9 (4.8)	2 (1.9)
Nervousness	19 (4.7)	11 (3.9)
Trauma	19 (4.7)	11 (3.9)
Hypotension	17 (4.2)	4 (1.4)
Libido Decreased	17 (4.2)	0 (0.0)
Abdominal pain	16 (3.9)	11 (3.9)
Urinary Tract Infection	14 (3.4)	7 (2.5)
Abnormal Vision	13 (3.2)	3 (1.1)
Infection	13 (3.2)	2 (0.7)
Anxiety	11 (2.7)	5 (1.8)
Arthralgia	10 (2.5)	5 (1.8)
Urinary Frequency	10 (2.5)	0 (0.0)

* Percentage corrected for gender

Adverse events occurring in patients aged >65 years at a frequency on paroxetine of ≥2.5% and at least twice that on placebo were: somnolence, asthenia, diarrhoea, constipation, impotence, tremor, decreased appetite, sweating, abnormal ejaculation, hypotension, libido decreased, abnormal vision, infection and urinary frequency.

To determine whether particular adverse events were reported relatively more frequently in elderly patients, the AEs reported in patients aged >65 years in studies 487, 625, 637 and 646 were compared to those reported from all of the placebo-controlled studies conducted with paroxetine (Table 9.8).

Table 9.8 Comparison of the Proportion of Elderly Patients (>65 years) with Emergent Adverse Events on Therapy by Preferred Term by Decreasing Order of Frequency on Paroxetine in Elderly Patients in Studies 487, 625, 637, 646, and in patients of all ages in the Entire Acute Placebo Controlled Paroxetine Studies Database

	Elderly Patients (>65 years) in Studies 487, 625, 637, 646		All patients in paroxetine placebo-controlled studies	
Preferred Term	**Paroxetine** N = 406 **n (%)**	**Placebo** N = 282 **n (%)**	**Paroxetine** N = 8481 **n (%)**	**Placebo** N = 5808 **n (%)**
Total with ≥ 1 AE	**286 (70.4)**	**174 (61.7)**	**6753 (79.6)**	**3983 (68.6)**
Somnolence	59 (14.5)	15 (5.3)	1384 (16.3)	330 (5.7)
Nausea	48 (11.8)	25 (8.9)	1745 (20.6)	564 (9.7)
Asthenia	48 (11.8)	15 (5.3)	1140 (13.4)	394 (6.8)
Headache	47 (11.6)	30 (10.6)	1885 (22.2)	1194 (20.6)
Diarrhoea	47 (11.6)	15 (5.3)	922 (10.9)	396 (6.8)
Constipation	45 (11.1)	8 (2.8)	710 (8.4)	218 (3.8)
Dry Mouth	40 (9.9)	19 (6.7)	959 (11.3)	335 (5.8)
Insomnia	39 (9.6)	24 (8.5)	1209 (14.3)	539 (9.3)
Dizziness	35 (8.6)	17 (6.0)	894 (10.5)	394 (6.8)
Impotence*	15 (8.0)	3 (2.8)	175 (5.4)	23 (1.0)
Tremor	30 (7.4)	2 (0.7)	561 (6.6)	82 (1.4)
Respiratory Disorder	27 (6.7)	21 (7.4)	732 (8.6)	519 (8.9)
Decreased Appetite	26 (6.4)	3 (1.1)	467 (5.5)	115 (2.0)
Sweating	25 (6.2)	5 (1.8)	684 (8.1)	140 (2.4)
Dyspepsia	24 (5.9)	11 (3.9)	410 (4.8)	257 (4.4)
Flatulence	20 (4.9)	10 (3.5)	235 (2.8)	136 (2.3)
Abnormal Ejaculation*	9 (4.8)	2 (1.9)	579 (17.8)	35 (1.6)
Nervousness	19 (4.7)	11 (3.9)	517 (6.1)	274 (4.7)
Trauma	19 (4.7)	11 (3.9)	333 (3.9)	175 (3.0)
Hypotension	17 (4.2)	4 (1.4)	49 (0.6)	28 (0.5)
Libido Decreased	17 (4.2)	0 (0.0)	578 (6.8)	97 (1.7)
Abdominal pain	16 (3.9)	11 (3.9)	355 (4.2)	224 (3.9)
Urinary Tract Infection	14 (3.4)	7 (2.5)	116 (1.4)	78 (1.3)
Abnormal Vision	13 (3.2)	3 (1.1)	202 (2.4)	51 (0.9)
Infection	13 (3.2)	2 (0.7)	434 (5.1)	282 (4.9)
Anxiety	11 (2.7)	5 (1.8)	361 (4.3)	195 (3.4)
Arthralgia	10 (2.5)	5 (1.8)	134 (1.6)	107 (1.8)
Urinary Frequency	10 (2.5)	0 (0.0)	161 (1.9)	49 (0.8)

*Percentage corrected for gender

Of the adverse experiences that occurred more frequently on paroxetine than placebo in elderly patients, most also occurred more frequently on paroxetine than placebo in the overall experience in all placebo-controlled studies. Adverse experiences with a greater difference in frequency of reporting between paroxetine and placebo in elderly patients than in patients of all ages in the entire acute placebo-controlled studies database were diarrhoea, constipation, impotence, hypotension, abnormal vision and infection. Adverse experiences for which the excess on paroxetine over placebo was less in elderly patients than in the overall experience were nausea, dry mouth, sweating and abnormal ejaculation. It is interesting to note that the excess on paroxetine over placebo of some "anti-cholinergic" events was less in elderly patients (dry mouth, sweating) while for others, including hypotension and constipation, the excess on paroxetine appeared greater in the elderly (although diarrhoea also occurred more frequently in the elderly). Overall, anticholinergic adverse events were not consistently reported at a larger excess over placebo in elderly patients receiving paroxetine than in all patients receiving paroxetine.

Events of particular interest – possibly suicide-related events and potentially withdrawal events

The number of elderly (>65 years) patients in studies 487, 625, 637 and 646 with possibly suicide-related adverse events was examined. Only 2 events (0.7%, 2/268) occurred in patients receiving paroxetine and none on placebo. One event was described as "mild", the other "severe", (Data Source Appendix 1, Table 3.01 and Table 3.04). The low percentage in the elderly patients is in agreement with the by-age analysis of such events shown in the original response, Sep 2003 (Table 9.9).

Table 9.9 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Age Group
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase)

Age Group	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.82 (0.57, 1.18)	0.31
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	31/1727 (1.8%)	17/1204 (1.4%)	1.28 (0.70, 2.32)	0.46
30-39 years	18/2550 (0.7%)	18/1728 (1.0%)	0.68 (0.35, 1.30)	0.24
40-49 years	12/2270 (0.5%)	11/1515 (0.7%)	0.73 (0.32, 1.65)	0.52
50-59 years	3/1152 (0.3%)	9/807 (1.1%)	0.23 (0.06, 0.86)	0.034
60-69 years	0/530 (0.0%)	0/381 (0.0%)		
70+ years	2/247 (0.8%)	0/172 (0.0%)		0.51

Adverse events that occurred during the taper and/or follow-up phases of studies 487, 625, 637 and 646 and identified as potentially withdrawal events were also recorded (Table 9.10), (Data Source: Appendix 1, Table 3.02 and Table 3.05).

Table 9.10 Number (%) of Patients with Adverse Events by Preferred Term Patients >65 years in Studies 487, 625, 637 and 646 All AEs Identified as Potentially Withdrawal Events* Taper and Follow-up Phase

Preferred Term	Paroxetine N = 268 n (%)	Placebo N =182 n (%)
Total number of patients with potentially withdrawal events	**17 (6.3)**	**17 (9.3)**
Dizziness	6 (2.2%)	2 (1.1%)
Headache	4 (1.5%)	2 (1.1%)
Nausea	3 (1.1%)	5 (2.7%)
Insomnia	2 (0.7%)	1 (0.5%)
Abnormal Dreams	2 (0.7%)	0 (0.0%)
Asthenia	1 (0.4%)	3 (1.6%)
Diarrhoea	1 (0.4%)	2 (1.1%)
Confusion	1 (0.4%)	1 (0.5%)
Nervousness	1 (0.4%)	1 (0.5%)
Tremor	1 (0.4%)	1 (0.5%)
Agitation	1 (0.4%)	0 (0.0%)
Somnolence	1 (0.4%)	0 (0.0%)
Sweating	1 (0.4%)	0 (0.0%)
Vertigo	1 (0.4%)	0 (0.0%)
Anxiety	0.(0.0%)	2 (1.1%)
Vomiting	0.(0.0%)	2 (1.1%)
Chills	0 (0.0%)	1 (0.5%)

* Potentially withdrawal event based on blinded manual review of all preferred terms.

In total, these events occurred at a higher frequency in patients who had received placebo and there was no suggestion that events that occurred in patients who had received paroxetine were any more severe than those in patients stopping placebo. No patient in the paroxetine group had a "severe" AE, and only 7 patients (2.6%) had a potentially withdrawal event of "moderate" maximum severity. One patient stopping placebo had a "severe" event, and 8 patients (4.4%) reported events of "moderate" severity.

Effect of co-morbidity and concomitant medications on AEs in elderly (>65 years) patients

The ten most frequently reported currently active medical conditions in the elderly population from studies 487, 625, 637, and 646 were: diabetes mellitus (12.9%), arthropathy (11.3%), cerebrovascular disorder (9.1%), osteoarthrosis (8.4%), headache (8.2%), hypertension (8.2%), hypothyroidism (8.2%), elevated cholesterol/triglycerides (7.8%), insomnia (6.9%), prostate disorder (6.0%).

Of the two elderly patients with possibly suicide-related events while receiving paroxetine, only one had any of the comorbid disorders listed above, and that was "headache", (Data Source: Appendix 1, Table 3.07).

The number of patients with potentially withdrawal events who also had the above comorbid conditions is shown in Table 9.11, (Data Source: Appendix 1, Table 3.08).

Table 9.11 Number (%) of Elderly Patients (>65 years) from Studies 487, 627, 637 and 646 with Potentially Withdrawal Events and Medical Condition
All AEs Identified as Potentially Withdrawal Events*
Taper and Follow-up Phase

	Paroxetine		Placebo	
	Number of patients with ≥ 1 withdrawal AE			
	n (%)	n (%)	n (%)	n (%)
Comorbid Condition	**Yes**	**No**	**Yes**	**No**
Diabetes mellitus	2/33 (6.1%)	15/235 (6.4%)	2/25 (8.0%)	15/157 (9.6%)
Arthropathy	2/29 (6.9%)	15/239 (6.3%)	3/22 (13.6%)	14/160 (8.8%)
Cerebrovascular Disorder	0/19 (0.0%)	17/249 (6.8%)	2/22 (9.1%)	15/160 (9.4%)
Osteoarthrosis	2/26 (7.7%)	15/242 (6.2%)	3/12 (25.0%)	14/170 (8.2%)
Headache	0/24 (0.0%)	17/244 (7.0%)	2/13 (15.4%)	15/169 (8.9%)
Hypertension	4/21 (19.0%)	13/247 (5.3%)	3/16 (18.8%)	14/166 (8.4%)
Hypothyroidism	4/21 (19.0%)	13/247 (5.3%)	3/16 (18.8%)	14/166 (8.4%)
Elevated Cholesterol/ Triglyceride	1/17 (5.9%)	16/251 (6.4%)	3/18 (16.7%)	14/164 (8.5%)
Insomnia	0/14 (0.0%)	17/254 (6.7%)	1/17 (5.9%)	16/165 (9.7%)
Prostate Disorder	2/14 (14.3%)	15/254 (5.9%)	3/13 (23.1%)	14/169 (8.3%)

* Potentially withdrawal event based on blinded manual review of all preferred terms.

Although the number of events that may be considered as potentially withdrawal events was small, the above data gave a suggestion that patients with hypertension and hypothyroidism were more likely to have such events. However no effect of treatment was observed. Such events occurred more frequently in patients with hypertension or hypothyroidism in both the paroxetine and placebo treatment groups.

The effect of comorbid conditions on the occurrence of anticholinergic events was also examined, (Table 9.12), (Data Source: Appendix 1, Table 3.03, Table 3.09). A patient was considered to have had an anticholinergic event if he/she had at least one of the following: dry mouth, thirst, sweating, tremor, extrapyramidal syndrome, bradycardia, hypotension, postural hypotension, or vasodilatation. (Constipation is usually considered to be an anticholinergic adverse event, but as diarrhoea occurred at a similar excess on paroxetine over placebo in this population as did constipation, constipation was not included).

Table 9.12 Number (%) of Elderly Patients (>65 years) from Studies 487, 627, 637 and 646 with Anti-Cholinergic Adverse Events and Medical Condition
On-Therapy plus 30 days follow-up

	Paroxetine		Placebo	
	Number of patients with ≥ 1 anticholinergic AE			
	n (%)	n (%)	n (%)	n (%)
Comorbid Condition	**Yes**	**No**	**Yes**	**No**
Diabetes mellitus	7/33 (21.2%)	59/235 (25.1%)	1/25 (4.0%)	16/157 (10.2%)
Arthropathy	6/29 (20.7%)	60/239 (25.1%)	3/22 (13.6%)	14/160 (8.8%)
Cerebrovascular Disorder	1/19 (5.3%)	65/249 (26.1%)	1/22 (4.5%)	16/160 (10.0%)
Osteoarthrosis	7/26 (26.9%)	59/242 (24.4%)	2/12 (16.7%)	15/170 (8.8%)
Headache	5/24 (20.8%)	61/244 (25.0%)	2/13 (15.4%)	15/169 (8.9%)
Hypertension	12/21 (57.1%)	54/247 (21.9%)	3/16 (18.8%)	14/166 (8.4%)
Hypothyroidism	12/21 (57.1%)	54/247 (21.9%)	3/16 (18.8%)	14/166 (8.4%)
Elevated Cholesterol/ Triglyceride	7/17 (41.2%)	59/251 (23.5%)	2/18 (11.1%)	15/164 (9.1%)
Insomnia	2/14 (14.3%)	64/254 (25.2%)	2/17 (11.8%)	15/165 (9.1%)
Prostate Disorder	3/14 (21.4%)	63/254 (24.8%)	0/13 (0.0%)	17/169 (10.1%)

Anticholinergic events (by the above definition) occurred more frequently in patients treated with paroxetine (24.6%, 66/268) than placebo (9.3%, 17/182). The presence of hypertension and hypothyroidism appeared to lead to an increased reporting of anticholinergic events, and cerebrovascular disorders to reduced reporting. However, the number of cases was small, and do not allow firm conclusions to be drawn.

The ten most frequently reported concomitant medications in the elderly population from studies 487, 625, 637, and 646 were: acetylsalicylic acid (31.1%), paracetamol (15.8%), vitamins (NOS) (12.4%), hydrochlorothiazide (10.9%), ibuprofen (8.0%), ranitidine (7.8%), levothyroxine (7.6%), conjugated estrogens (7.3%), enalapril (7.1%).

Of the two patients with possibly suicide-related events, only one took any of the above medications concomitantly with study drug. That patient took paracetamol after the adverse event (Data Source: Appendix 1: Table 3.10).

Information regarding the number of patients who received any of the above medications before or after having events that were potentially withdrawal events is shown in Table 9.13, (Data Source: Appendix 1, Table 3.11).

Table 9.13 Number (%) of Elderly Patients (>65 years) from Studies 487, 627, 637 and 646 with Potentially Withdrawal Events and Concomitant Medication
All AEs Identified as Potentially Withdrawal Events*
Taper and Follow-up Phase

		Number of patients with ≥ 1 withdrawal AE		
	Treatment	**n (%)**	**n (%)**	**n (%)**
Concomitant Medication		**Yes – Med before AE**	**Yes – Med after AE**	**No**
Acetylsalicylic acid	Paroxetine	5/84 (6.0%)	0/84 (0.0%)	12/184 (6.5%)
	Placebo	4/56 (7.1%)	0/56 (0.0%)	13/126 (10.3%)
Paracetamol	Paroxetine	7/50 (14.0%)	2/50 (4.0%)	9/218 (4.1%)
	Placebo	5/21 (23.8%)	1/21 (4.8%)	11/161 (6.8%)
Vitamins NOS	Paroxetine	3/35 (8.6%)	0/35 (0.0%)	14/233 (6.0%)
	Placebo	2/21 (9.5%)	1/21 (4.8%)	14/161 (8.7%)
Hydrochlorothiazide	Paroxetine	0/26 (0.0%)	0/26 (0.0%)	17/242 (7.0%)
	Placebo	2/23 (8.7%)	0/23 (0.0%)	15/159 (9.4%)
Ibuprofen	Paroxetine	1/19 (5.3%)	0/19 (0.0%)	16/249 (6.4%)
	Placebo	2/17 (11.8%)	0/17 (0.0%)	15/165 (9.1%)
Ranitidine	Paroxetine	2/26 (7.7%)	1/26 (3.8%)	14/242 (5.8%)
	Placebo	1/9 (11.1%)	0/9 (0.0%)	16/173 (9.2%)
Levothyroxine	Paroxetine	4/19 (21.1%)	0/19 (0.0%)	13/249 (5.2%)
	Placebo	3/15 (20.0%)	0/15 (0.0%)	14/167 (8.4%)
Conjugated Estrogens	Paroxetine	1/23 (4.3%)	0/23 (0.0%)	16/245 (6.5%)
	Placebo	1/10 (10.0%)	0/10 (0.0%)	16/172 (9.3%)
Enalapril	Paroxetine	0/16 (0.0%)	0/16 (0.0%)	17/252 (6.7%)
	Placebo	1/16 (6.3%)	0/16 (0.0%)	16/166 (9.6%)

No obvious relationship was noticed between any of the most frequently taken concomitant medications and the occurrence of potentially withdrawal events in the elderly (>65 years).

The effect of those concomitant medications on the occurrence was anticholinergic events was also examined, (Table 9.14), (Data Source: Appendix 1, Table 3.12).

Table 9.14 Number (%) of Elderly Patients (>65 years) from Studies 487, 627, 637 and 646 with Anticholinergic Events and Concomitant Medication
On-therapy plus 30 days post-therapy

		Number of patients with ≥ 1 withdrawal AE		
	Treatment	**n (%)**	**n (%)**	**n (%)**
Concomitant Medication		**Yes – Med before AE**	**Yes – Med after AE**	**No**
Acetylsalicylic acid	Paroxetine	29/84 (34.5%)	4/84 (4.8%)	34/184 (18.5%)
	Placebo	6/56 (10.7%)	1/56 (1.8%)	10/126 (7.9%)
Paracetamol	Paroxetine	14/50 (28.0%)	7/50 (14.0%)	48/218 (22.0%)
	Placebo	5/21 (23.8%)	1/21 (4.8%)	11/161 (6.8%)
Vitamins NOS	Paroxetine	11/35 (31.4%)	0/35 (0.0%)	55/233 (23.6%)
	Placebo	0/21 (0.0%)	2/21 (9.5%)	15/161 (9.3%)
Hydrochlorothiazide	Paroxetine	5/26 (19.2%)	0/26 (0.0%)	61/242 (25.2%)
	Placebo	2/23 (8.7%)	0/23 (0.0%)	15/159 (9.4%)
Ibuprofen	Paroxetine	7/19 (36.8%)	1/19 (5.3%)	58/249 (23.3%)
	Placebo	2/17 (11.8%)	0/17 (0.0%)	15/165 (9.1%)
Ranitidine	Paroxetine	3/26 (11.5%)	2/26 (7.7%)	61/242 (25.2%)
	Placebo	1/9 (11.1%)	0/9 (0.0%)	16/173 (9.2%)
Levothyroxine	Paroxetine	11/19 (57.9%)	0/19 (0.0%)	55/249 (22.1%)
	Placebo	4/15 (26.7%)	0/15 (0.0%)	13/167 (7.8%)
Conjugated Estrogens	Paroxetine	8/23 (34.8%)	0/23 (0.0%)	58/245 (23.7%)
	Placebo	4/10 (40.0%)	0/10 (0.0%)	13/172 (7.6%)
Enalapril	Paroxetine	1/16 (6.3%)	0/16 (0.0%)	65/252 (25.8%)
	Placebo	0/16 (0.0%)	0/16 (0.0%)	17/166 (10.2%)

A high proportion of patients taking levothyroxine had anticholinergic events, and a relatively low proportion taking enalapril had such events, but there was no medication that clearly produced an increase risk of anticholinergic events in elderly patients when taken with paroxetine but not with placebo. These observations cannot be considered as definitive however, as they suffer from the shortcoming of small numbers that was mentioned previously.

9.4. Benefit-Risk of Paroxetine in the Elderly (>65 years)

The preceding sections demonstrate that paroxetine has been proven to be an efficacious treatment in elderly patients with depression. Examination of the adverse events observed in elderly patients treated with paroxetine revealed no appreciable difference from those seen in patients in the general adult population, and elderly patients were at no greater risk of developing possibly suicide-related events or withdrawal events. In addition, an examination of the most frequently used concomitant medications and the most commonly occurring comorbid medical conditions in elderly patients in studies 487, 625, 637 and 646 revealed no interaction of concern regarding the occurrence of possibly suicide-related events, withdrawal events or anticholinergic events. In summary, the benefit-risk balance of paroxetine in elderly patients (>65 years) is clearly positive. The demonstrated efficacy and tolerability of paroxetine in the elderly are important since surveys have shown elderly depression to be highly prevalent within the community with 10-15% of elderly outpatients and up to 30% of elderly inpatients having depression, [Katona,1996].

9.5. References

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