5. QUESTION 5

Provide the data from the analysis of the clinical trial data to identify possible risk factors for suicidal behaviour, self-harm and hostility in a suitable format to be able to see all interaction terms regardless of level of significance. This should include a table with the odds-ratio and confidence intervals for each of treatment risk factor interaction. This clear presentation will enable trends in data to be examined.

Since suicide-related adverse events were possibly over represented in the paroxetine group in the youngest age group in the adult studies, it is suggested that the MAHs should merge data from placebo controlled adult and paediatric studies in an age-specific risk factor analysis.

Response

5.1. Possible risk factors for possibly suicide-related events, self-harm and hostility - Tabulations

Tables with the odds ratio and confidence intervals for each treatment risk factor interaction are given in Appendix 5.

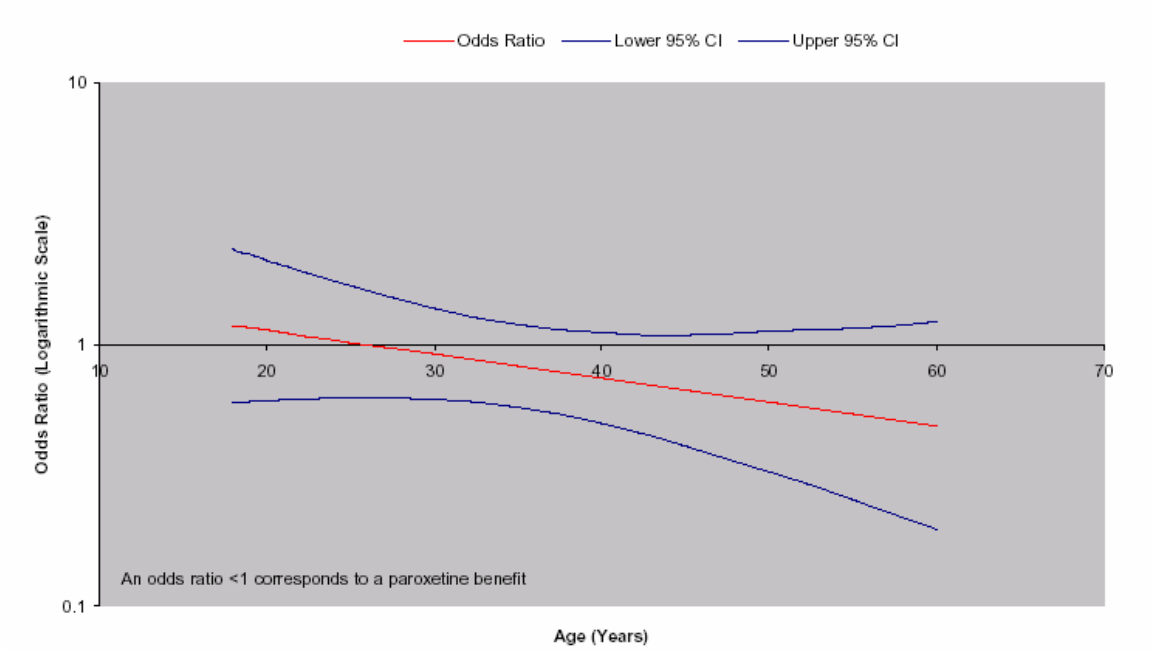
5.2. Possibly suicide-related events by age

5.2.1. Placebo controlled studies

The entry criteria for paroxetine adult placebo-controlled trials prevented enrollment of patients aged < 18 years of age. The paroxetine paediatric placebo-controlled studies between them gave information on patients aged 7 to 18 years. There was no trial that permitted enrollment of both paediatric and adult patients. Until now, information from those two study populations, and hence paediatric and adult patients, has been regarded separately. However, in response to the question posed, an analysis has been performed using merged data from the placebo-controlled paediatric and adult paroxetine studies.

As described in the original response (Sept 2003), Figure 5.1 shows the odds ratio (paroxetine relative to placebo) and the 95% confidence interval for possibly suicide-related adverse events by age occurring in paroxetine adult placebo-controlled studies.

Figure 5.1 Odds Ratio (Paroxetine Relative to Placebo) and 95% CI for Possibly Suicide-Related Adverse Events by Age
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase)



In the adult placebo-controlled trials, although the odds ratio indicates that there was a slightly greater risk of having possibly suicide-related events on paroxetine than on placebo below the age of approximately 25 years, this was not statistically significant. Above the age of approximately 25 years, the odds ratio indicated a reduced risk of having possibly suicide-related events on paroxetine than on placebo and although this too was not statistically significant, it approached significance around the 40 year mark. In summary, there was no compelling evidence of a treatment effect at any particular age from these adult studies.

The incidence of on-therapy possibly suicide-related events by treatment group and age group was summarised as shown in Table 5.1. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test.

Table 5.1 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

Overall (i.e. across all age groups) the incidence of on-therapy possibly suicide-related events was 0.8% in the paroxetine treatment group and 0.9% in the placebo group. Thirty one (31) of the 66 (47%) events in the paroxetine group and 17 of the 55 (31%) events in the placebo group occurred in the 18-29 years age group. In the 18-29 years age group, there was a greater incidence of possibly suicide-related events in the paroxetine treatment group (31/1727, 1.8%) compared to the placebo group (17/1204, 1.4%) but this difference was not statistically significant (OR 1.28, 95% CI 0.70, 2.32, P=0.46). In the 50-59 years age group, there was a lower incidence of possibly suicide-related events in the paroxetine treatment group (3/1152, 0.3%) than in the placebo group (9/807, 1.1%) and this difference was statistically significant (OR 0.23 , 95% CI 0.06, 0.86, P=0.034).

The suggestion of a greater incidence of possibly suicide-related events in the paroxetine treatment group in patients aged 18-29 years was in the same direction as observations in the paediatric placebo-controlled trials in which (as shown below) there was a higher incidence of possibly suicide-related events in patients aged ≥ 16 years and aged 12-15 years (although not in patients aged < 12 years) in the paroxetine treatment group compared to the placebo group.

The incidence of possibly suicide-related events occurring in the "on-therapy period" by treatment group and age group in paroxetine paediatric placebo-controlled trials is summarised in Table 5.2. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test. Note that there is no figure showing the odds ratio for possibly suicide-related adverse events by age since there was no significant linear effect of age in the paediatric placebo-controlled trials population.

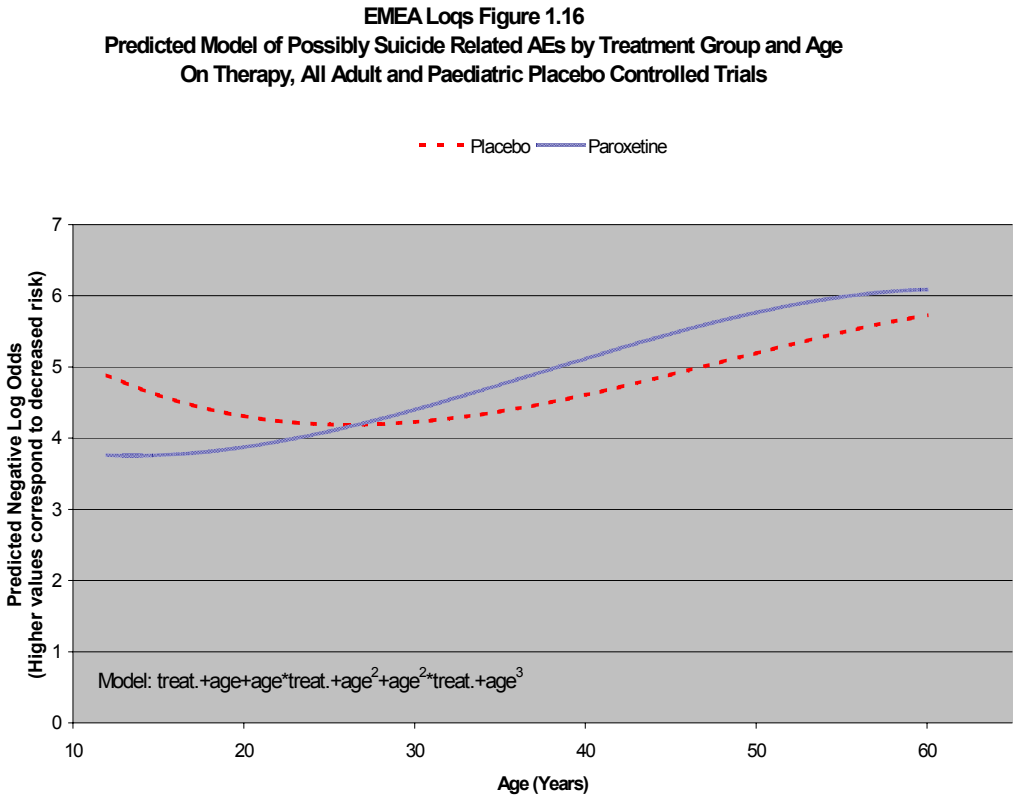
**Table 5.2 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Age Group
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase)**

Age Group	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	18/738 (2.4%)	7/647 (1.1%)	2.29 (0.95, 5.51)	0.069
<12 years	0/205 (0.0%)	0/194 (0.0%)		
12-15 years	10/329 (3.0%)	5/269 (1.9%)	1.66 (0.56, 4.90)	0.44
≥16 years	8/204 (3.9%)	2/184 (1.1%)	3.71 (0.78, 17.72)	0.11

Overall (i.e. across the defined age groups), in the paediatric placebo-controlled trials the incidence of on-therapy possibly suicide-related events was 2.4% in the paroxetine treatment group and 1.1% in the placebo group (OR 2.29, 95% CI 0.95, 5.51, P=0.069). No possibly suicide-related events were seen on-therapy in the under 12 year age group in either of the treatment groups. As mentioned above, in both the 12-15 year age group and the ≥16 year age group, there was a higher incidence of events in the paroxetine treatment group compared to the placebo group, although the differences between the treatment groups were not statistically significant.

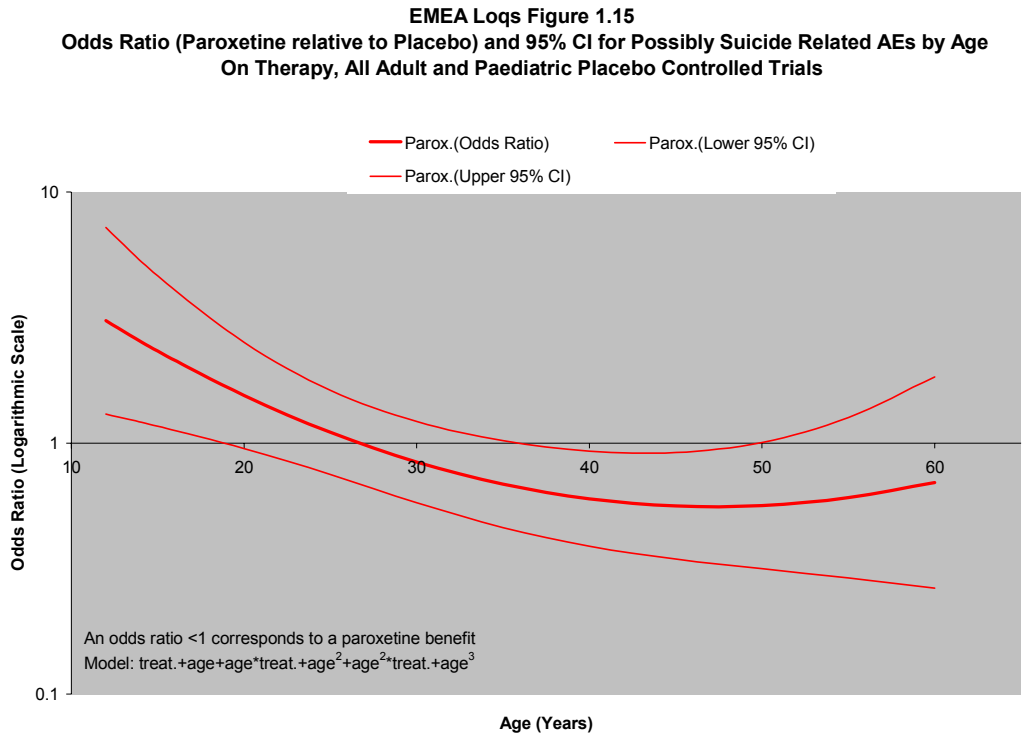
The data from the adult and paediatric placebo-controlled trials have now been analysed together and Figure 5.2 shows the fitted model modelling these data as accurately as possible. Neither a linear model (i.e. a straight line) nor a quadratic model (i.e. a curve with one turning point) were particularly suitable. Instead, a cubic model (i.e. a curve with two turning points was required to summarise the data.

**Figure 5.2 Predicted Model of Possibly Suicide-Related Events by Treatment Group and Age
All Adult and Paediatric Placebo Controlled Trials
On Therapy**



In Figure 5.2, a higher value corresponds to decreased risk. It can be seen that on paroxetine the risk is highest in the teenage years, and then reduces such that by around age 27 the estimated risk is equal to placebo, and thereafter the risk on paroxetine is lower than on placebo. Odds ratio and 95% confidence intervals for possibly suicide-related events (paroxetine relative to placebo) by age are plotted as Figure 5.3.

**Figure 5.3 Odds Ratio (Paroxetine relative to Placebo) and 95% C.I. for Possibly Suicide-Related Events by Age
All Adult and Paediatric Placebo Controlled Trials
On Therapy**



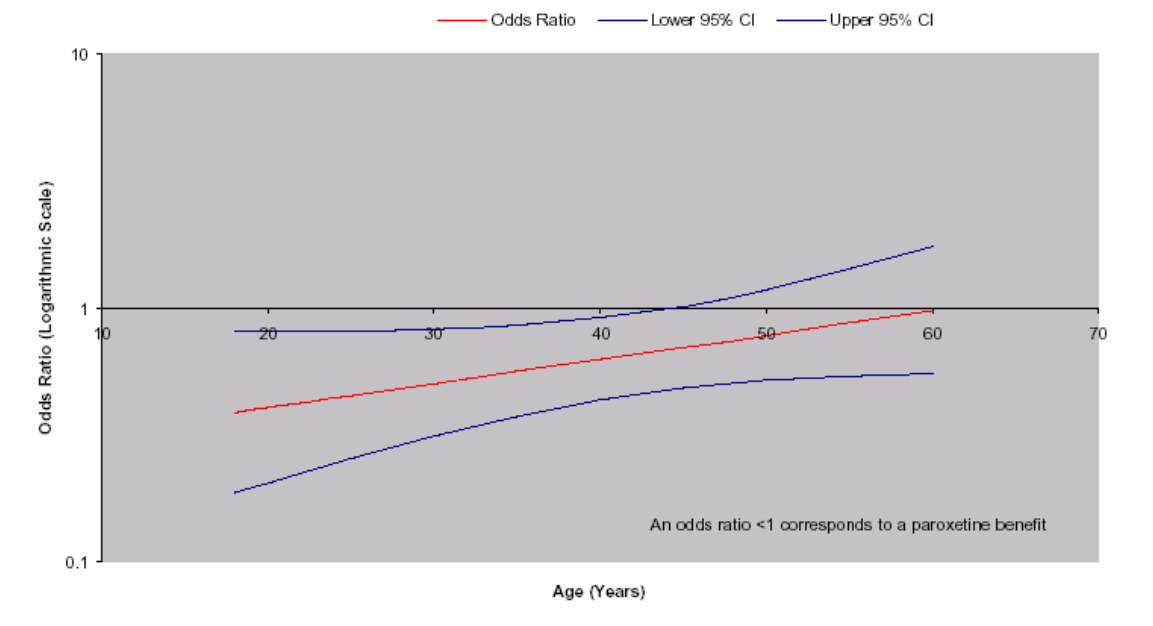
The odds ratio of paroxetine relative to placebo from placebo-controlled trials indicate increased risk in younger patients. As indicated in Figure 5.2, the risk on paroxetine reduces such that the estimated risk on paroxetine is equal to placebo at approximately 27 years of age, however the 95% confidence intervals around the odds ratio are wide. Taking the 95% C.I.s into account, the data from the placebo-controlled studies indicate a significant increase in risk on paroxetine compared to placebo in patients aged under 18 years, and significantly less risk in patients aged mid 30's to approximately 50 years.

5.2.2. Active Control Studies

5.2.2.1. Comparisons against active comparators

As was also shown in the original response, Figure 5.4 shows the odds ratio (paroxetine relative to active comparator) and the 95% confidence interval for possibly suicide-related adverse events that occurred in adult active control trials by age.

Figure 5.4 Odds Ratio (Paroxetine Relative to Active Comparator) and 95% CI for Possibly Suicide-Related Adverse Events by Age
Adult Active Controlled Trials
On-Therapy



The odds ratio indicated a reduced risk of having possibly suicide-related events on paroxetine than on active comparator across the age range of the active controlled studies, and that the benefit of treatment with paroxetine was greatest in young adults. This reduced risk, seen on paroxetine compared to active control medication, was statistically significant up until the mid-40's age mark.

The incidence of on-therapy possibly suicide-related events by treatment group and age group is summarised in the following table. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test.

**Table 5.3 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Age Group
Adult Active Controlled Trials
On-Therapy**

Age Group	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.66 (0.46, 0.95)	0.031
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	10/969 (1.0%)	20/779 (2.6%)	0.40 (0.18, 0.85)	0.016
30-39 years	13/1544 (0.8%)	10/1146 (0.9%)	0.96 (0.42, 2.21)	1.00
40-49 years	12/1647 (0.7%)	13/1182 (1.1%)	0.66 (0.30, 1.45)	0.31
50-59 years	9/1038 (0.9%)	14/835 (1.7%)	0.51 (0.22, 1.19)	0.14
60-69 years	7/831 (0.8%)	5/626 (0.8%)	1.06 (0.33, 3.34)	1.00
70+ years	4/457 (0.9%)	1/390 (0.3%)	3.43 (0.38, 30.86)	0.38
Unknown	0/32 (0.0%)	0/5 (0.0%)		

Overall (i.e. across all age groups) the incidence of on-therapy possibly suicide-related events was 0.8% in the paroxetine treatment group and 1.3% in the active comparator group and this difference was statistically significant (OR 0.66, 95% CI 0.46, 0.95, P=0.031). Possibly suicide-related events were seen throughout the range of age groups in both the paroxetine and active comparator treatment groups. In the 18-29 year age group, there was a lower incidence of possibly suicide-related events in the paroxetine treatment group (10/969, 1.0%) than in the active comparator group (20/779, 2.6%) and this difference was statistically significant (OR 0.40 , 95% CI 0.18, 0.85, P=0.016).

5.2.2.2. Comparison against fluoxetine

As can be seen in Table 5.4, in the adult active control studies, most of the difference in incidence of possibly suicide-related events between paroxetine and the comparators arose from studies of paroxetine in comparison with other SSRIs.

**Table 5.4 Incidence of Possibly Suicide-Related Events by Treatment Group and Control Medication Class
Adult Active Control Trials
On-Therapy**

Control Medication Class		Paroxetine	Comparator	Odds Ratio (95% CI)	P value
Overall	n/N (%)	55/6522 (0.8%)	63/4969 (1.3%)	0.66 (0.46 , 0.95)	0.031
Tricyclic	n/N (%)	26/2953 (0.9%)	32/2754 (1.2%)	0.76 (0.45 , 1.27)	0.29
SSRI	n/N (%)	14/1200 (1.2%)	24/1218 (2.0%)	0.59 (0.30, 1.14)	0.14
Tetracyclic	n/N (%)	2/527 (0.4%)	4/518 (0.8%)	0.49 (0.09 , 2.68)	0.45
Benzodiazepine	n/N (%)	0/76 (0.0%)	0/77 (0.0%)		
Other	n/N (%)	13/1766 (0.7%)	3/402 (0.7%)	0.99 (0.28 , 3.48)	1.00

Within that group of studies, comparisons were largely of paroxetine against fluoxetine. Of the 1200 patients treated with paroxetine and 1218 patients treated with SSRIs in active control studies of paroxetine against an SSRI, 948 of the paroxetine treated patients and 947 of the patients receiving an SSRI participated in studies of paroxetine versus fluoxetine (Table 5.5).

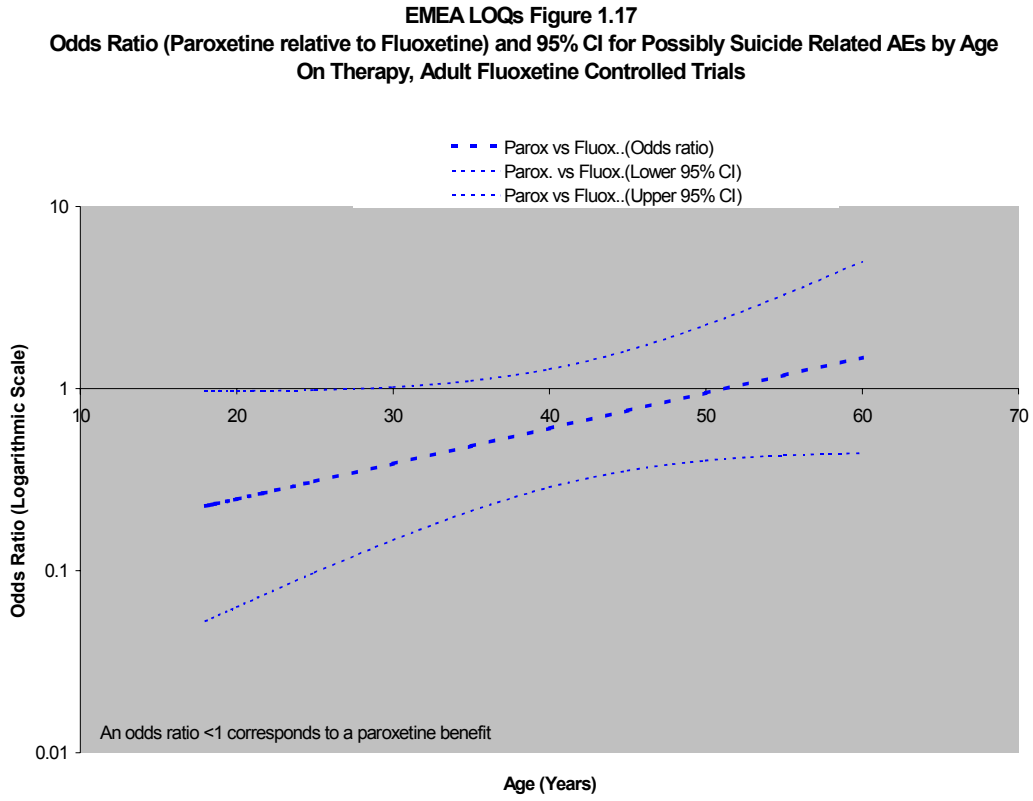
In the studies comparing paroxetine and fluoxetine, the overall incidence of possibly suicide-related events was 1.4% (13/948) in patients receiving paroxetine, and 2.1% (20/947) in patients receiving fluoxetine. Similar to the observation in placebo-controlled studies, the age group with the highest incidence of possibly suicide-related events was 18-29 years.

Table 5.5 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Age Group
Adult Active Controlled Trials Comparing Paroxetine and Fluoxetine On-Therapy

Age Group	Paroxetine n/N (%)	Fluoxetine n/N (%)	OR (95% CI)	P value
Overall	13/948 (1.4%)	20/947 (2.1%)	0.64 (0.32, 1.30)	0.23
18-29 years	3/150 (2.0%)	6/172 (3.5%)	0.56 (0.14, 2.30)	0.51
30-39 years	3/270 (1.1%)	6/257 (2.3%)	0.47 (0.12, 1.90)	0.33
40-49 years	3/251 (1.2%)	4/276 (1.4%)	0.82 (0.18, 3.71)	1.00
50-59 years	1/141 (0.7%)	2/136 (1.5%)	0.48 (0.04, 5.34)	0.62
60-69 years	1/80 (1.3%)	2/64 (3.1%)	0.39 (0.03, 4.43)	0.59
70+ years	2/56 (3.6%)	0/42 (0.0%)		0.51

The odds ratio (paroxetine relative to fluoxetine) and 95% confidence intervals for possibly suicide related events by age are shown in Figure 5.5.

Figure 5.5 Odds Ratio (Paroxetine Relative to Fluoxetine) and 95% CI for Possibly Suicide-Related Events by Age
Adult Active Controlled Trials Comparing Paroxetine and Fluoxetine On-Therapy



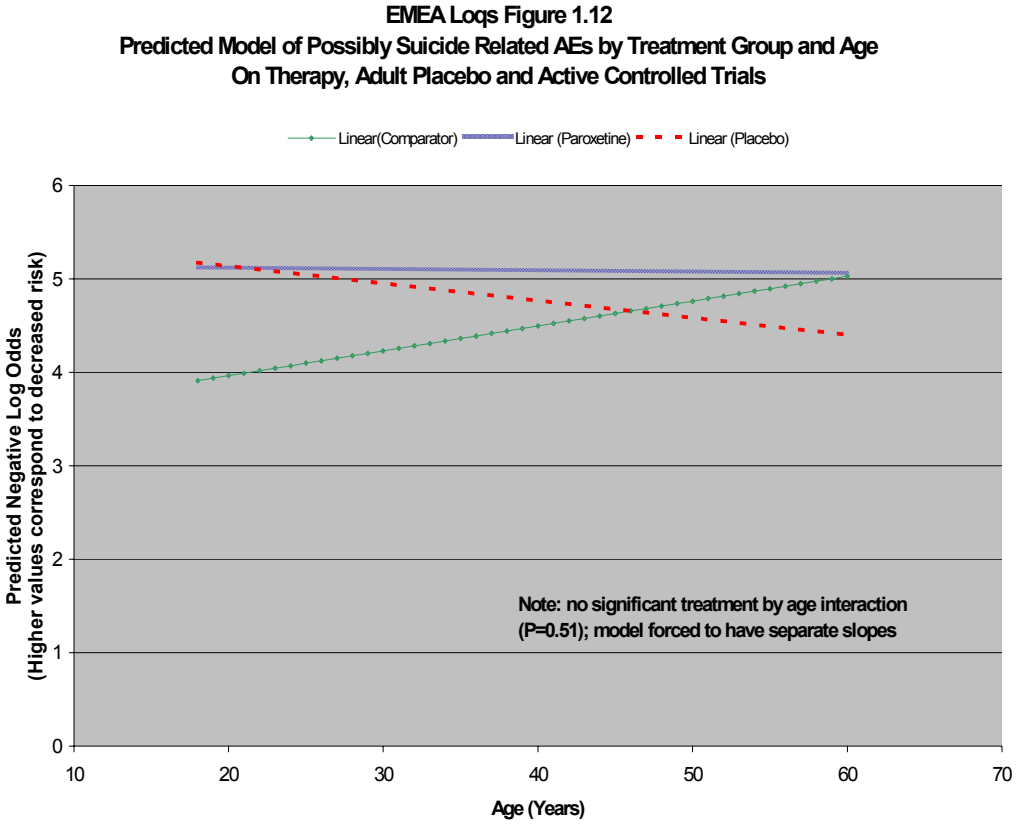
The estimated odds ratio indicates a lower risk of having a possibly suicide-related event on paroxetine than fluoxetine, with this lower risk being most apparent in young adults.

Although no studies have been conducted comparing paroxetine and fluoxetine in patients aged <18 years, the above observation, together with the consistent data in adolescents and young adults from paediatric and adult studies with paroxetine, suggest that fluoxetine is associated with a greater risk of possibly suicide-related events than paroxetine in young adults , and possibly also in adolescents.

5.2.2.3. Comparisons against active comparators and placebo.

Studies with a three arm design that allowed the opportunity for direct comparison of paroxetine with an active comparator and placebo within the same study were examined (Figure 5.6).

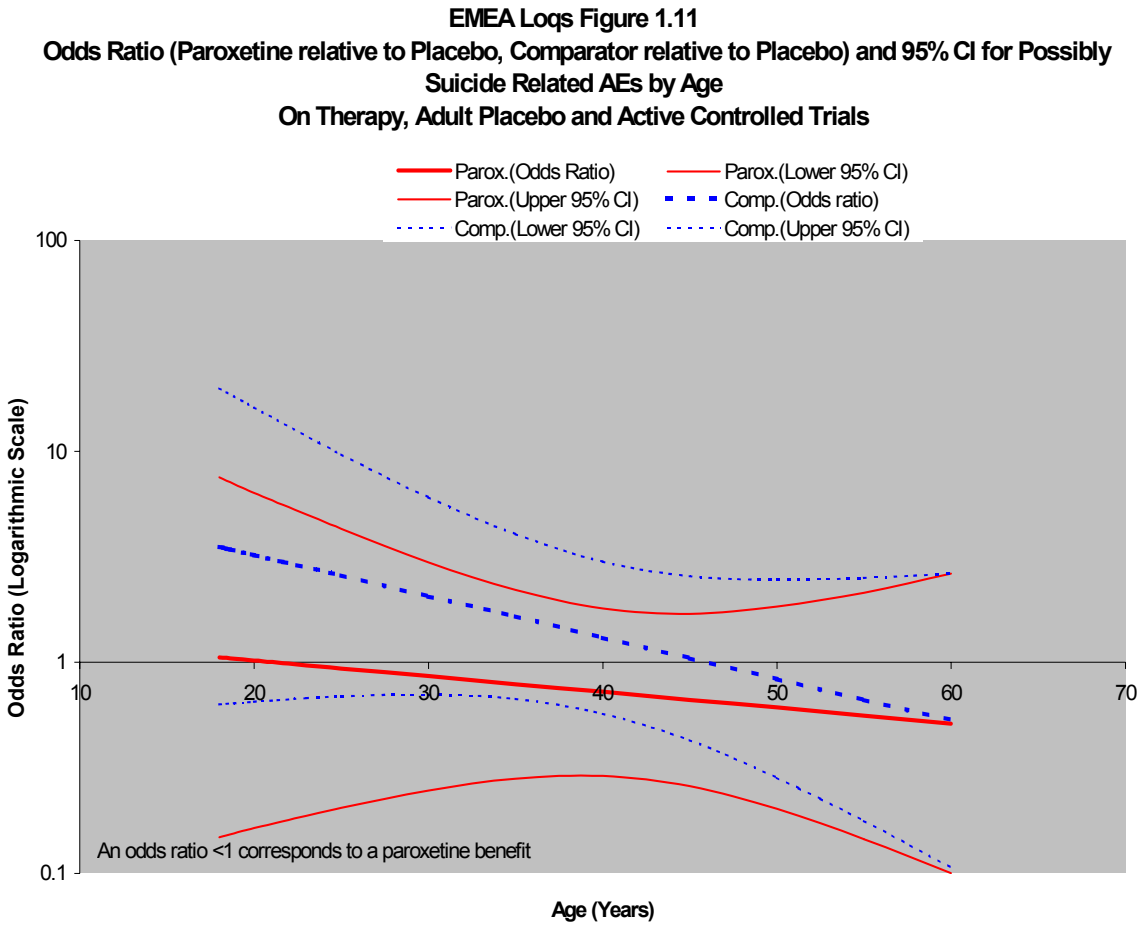
Figure 5.6 Possibly Suicide-Related Events by Treatment Group and by Age Adult Placebo and Active Controlled Trials On-Therapy



In this figure, higher values indicate lower risk. In these studies involving a total of 4227 patients, in which paroxetine (n=1637) was compared directly with both active comparator (n=1542) and placebo (n=1048), paroxetine was associated with less risk of possibly suicide-related events than active comparators across the range of ages studied, the difference from active comparators being greatest in young adults. The active comparators employed in these studies were fluoxetine, clomipramine, imipramine, amitriptyline, maprotiline, mianserin and alprazolam. In these studies, there appeared to be little change in the risk associated with paroxetine across the age range, whereas the risk associated with placebo increased with age. Paroxetine was associated with less risk of possibly suicide-related events than placebo across nearly the entire range of ages studied, the difference from placebo being greatest in older adults.

Figure 5.7 shows odds ratio of paroxetine and of active comparators relative to placebo, by age. In these 3-arm studies, paroxetine had a similar risk to placebo at approximately 20 years of age, and reduced risk compared to placebo above the age of 20. The active comparators were associated with higher risk than paroxetine up to 60 years of age, the excess risk relative to paroxetine being greatest in young adults. However the confidence intervals are quite wide.

Figure 5.7 Odds Ratio (Paroxetine relative to Placebo, Comparator relative to Placebo) and 95% C.I. for Possibly Suicide Related Events by Age Adult Placebo and Active Controlled Trials On-Therapy



5.2.3. Conclusions

Assessment of the risk of possibly suicide-related events by age in paediatric and adult placebo controlled trials indicated an increased risk of such events in younger patients treated with paroxetine, and particularly in patients under the age of 18. However, adult active control studies showed that the risk with paroxetine was lower than that from the active comparators, particularly in younger patients. Studies that compared paroxetine with fluoxetine indicated that paroxetine is associated with a lower risk of possibly suicide-related events in young adults than fluoxetine.

The MHRA has recently contraindicated the use of all but one SSRI (and the SSRI/SNRI venlafaxine) in children and adolescents with depression. The exception is fluoxetine. The finding that the risk of possibly suicide-related events was greater with fluoxetine than paroxetine, particularly in young adults, brings new information regarding the relative benefit/risk of fluoxetine and paroxetine in young adults, and by projection, in adolescents.