3. QUESTION 3: RISK FACTORS OF SELF-HARM, HOSTILITY AND POSSIBLY SUICIDE-RELATED EVENTS FROM ALL AVAILABLE SOURCES

Analysis of all data relating to the risk of self-harm, hostility and suicidal behaviour to identify risk factors such as:

- *Age*
- *Gender*
- *Severity of disease*
- *Dose*
- *Indication(s)*
- *Previous psychiatric/neurodevelopmental history*
- *Previous/concomitant pharmacotherapies*
- *Pharmacogenetic factors*

Response

3.1. Introduction

The analysis of risk factors for possibly suicide-related, self-harm and hostility events encompassed clinical trial data from the central R&D aggregated database (see Question 2, Section 2.3.1 for a description of the clinical trials dataset) and data obtained from post-marketing reports.

3.2. Clinical Studies

This section presents the analysis of the clinical trial data from the central R&D aggregated database.

3.2.1. Methodology of risk factor analysis

The Statistical Appendix for the analysis of risk factors for the clinical trial data can be found in Appendix 3, along with tabulations of incidence and incidence density of events by risk factor.

For each of the defined populations (adult placebo-controlled, adult active-controlled and paediatric placebo controlled trials) the effect of the following covariates on each of the three events of interest (possibly suicide-related events, self harm and hostility) were considered:

- Age
- Gender

- Race (white, black, other) i.e. pharmacogenetic factors
- Severity of disease. CGI - Severity of Illness ratings were split into three groups "normal" (scores of 1 or 2), "mildly to moderately ill" (scores of 3 or 4) and "severely ill" (scores of 5 or 6).
- Indication (Depression, GAD, OCD, Panic, PMDD, PTSD, SAD)
- Formulation (Immediate Release [IR] vs Controlled Release [CR] vs IR&CR studies). This covariate was not included for the paediatric placebo-controlled trials since all of these studies used paroxetine IR.
- Previous psychiatric history: for studies where medical history was coded, medical history terms where the preferred term or the verbatim contained the text string "suic", "overdos", "over dos" or "over-dos" were identified; however, cases where the events were accidental/unintentional were excluded. Note that cases where psychiatric history was not assessed or where medical history terms were not coded were classed as "absent".
- Previous / concomitant pharmacotherapies (psychotropic medication taken prior to randomisation). Note that cases where prior medications were not recorded or not coded were classed as "absent".
- Class of active control medication (this applies only to the adult active-controlled studies. Active comparators were grouped by class. Five groups were identified - tricyclics, tetracyclics, SSRIs, benzodiazepines, Other).
- Baseline suicidal ideation (HAM-D Item 3 ≥3 or MADRS Item 10 ≥3 at baseline). Note that cases from studies where the HAM-D or the MADRS were not used or cases where Item 3 of the HAM-D or Item 10 of the MADRS were not assessed were classed as "absent".
- Agitation at baseline (HAM-D Item 9 score ≥2 at baseline). Note that cases from studies where the HAM-D was not used or cases where Item 9 of the HAM-D was not assessed were classed as "absent".

With the exception of age (which was modelled as a continuous covariate) each covariate was considered as a categorical variable (i.e. not accounting for any specific order). If any covariate did not converge in the model then the categories were collapsed as appropriate.

The covariates were tested in a model building approach using a backwards elimination process at a 5% level of significance (i.e. all covariates were included in the model, then at each step the least significant covariate was removed one at a time until all the remaining covariates were statistically significant at the 5% level). The treatment effect was then added to the model adjusting for the relevant baseline covariates. The final set of covariates included at this stage constituted the "base model".

Treatment by covariate interactions were then assessed by including each in the base model (including treatment) one at a time and determining statistical significance at the 5% level.

For the possibly suicide-related and self harm events, once the base model had been selected, the following treatment-dependent covariates were also considered:

- On-therapy adverse event of agitation prior to the event (i.e. all adverse events coded to a preferred term of "agitation")
- On-therapy adverse event of hyperkinesia prior to the event (i.e. all adverse events coded to a preferred term of "hyperkinesia")
- On-therapy adverse event of hostility prior to the event (i.e. all adverse events meeting the definition of "hostility" as per Question 2, Section 2.3.6.1)
- Early emergent agitation, i.e. change from HAM-D Item 9 score of 0 or 1 at baseline to ≥2 within the first 28 days of treatment and prior to the event

No treatment-dependent covariates were considered for the hostility events.

The model building utilised a forward selection method with a significance level of 5%, i.e. each treatment-dependent covariate was added in turn to the base model (excluding treatment) and at each step, the covariate that gave the most statistically significant result was included in the model. This continued until all statistically significant terms were included in the final model. The treatment effect was then added to the model adjusting for all relevant covariates.

For the fixed dose depression studies, the effect of dose was assessed for the adult placebo-controlled trials, including dose in the model as a categorical variable. For the purpose of combining data from CR and IR studies, the CR dose was divided by 1.25 to give an approximately equivalent IR dose (i.e. 25mg CR is approximately equivalent to 20mg IR). The effect of dose was not modelled for any indications other than depression, because there were too few events for this to be assessed.

3.2.2. Risk factors of possibly suicide-related events

3.2.2.1. Adult placebo-controlled trials

The following baseline covariates were statistically significant at the 5% level for the adult placebo-controlled trials population, i.e. each had a significant effect on the risk of having a possibly suicide-related event, irrespective of whether patients were treated with paroxetine or placebo. When treatment effect was added to the base model, it did not have a significant effect.

Table 3.1 Statistically significant baseline covariates for possibly suicide-related adverse events
Adult placebo-controlled trials

Covariate	Odds Ratio Descriptor	Odds Ratio (95% CI)	P-value
Age	Per year increase	0.95 (0.93, 0.96)	<0.001
Indication	Depression:Other*	7.93 (4.82, 13.06)	<0.001
Formulation	CR:IR CR&IR:IR	0.23 (0.10, 0.54) 0.28 (0.12, 0.65)	<0.001 0.003
Psychiatric History	Absent:Present	0.14 (0.04, 0.45)	0.001
Psychotropic Medication	No:Yes	0.27 (0.19, 0.40)	<0.001
Baseline Suicidal Ideation	Absent:Present	0.28 (0.18, 0.43)	<0.001
Baseline Agitation	Absent:Present	2.14 (1.15, 3.96)	0.016
Treatment	Paroxetine:Placebo	0.88 (0.61, 1.28)	0.512

* includes GAD, OCD, PMDD, PTSD, Panic and SAD
Data Source: Appendix 3, Statistical Appendix

In the case of age, the odds ratio of 0.95 indicates that in the placebo-controlled trials population, for each additional year of age, the odds of a possibly suicide-related event are 0.95 times less likely. For other effects, the odds are presented for one category of a variable relative to another, e.g. the odds of a possibly suicide-related event were nearly eight times greater in depression trials than in the studies conducted in other indications. Similarly, patients with a previous psychiatric history, prior use of psychotropic medication and baseline suicidal ideation all had an increased risk of a possibly suicide-related event. Regarding formulation, an increased risk of a possibly suicide-related event was seen in the IR studies compared to the CR studies, and in the IR studies compared to the studies involving both CR and IR. However, this increased risk in the IR studies was seen in both the paroxetine and the placebo treatment arms and is therefore attributable to the characteristics of the study designs rather than to the formulation itself.

The main effect of baseline agitation was only found to be a significant covariate when indication was also included in the model; this implies an association between indication and baseline agitation, independent of treatment. In depression trials, possibly suicide-related events were reported by 2.1% of patients (88/1433) without agitation at baseline and by 0.8% of patients (11/1405) who were diagnosed with agitation at baseline, i.e. patients who were agitated upon entry to a depression study appeared to be at a lower risk of a possibly suicide-related event. In the indications other than depression, possibly suicide-related events were reported by 0.2% of patients (21/8675) without agitation at baseline and by 1.3% of patients (1/76) who did have agitation at baseline.

The following baseline covariates and treatment-dependent covariates were statistically significant at the 5% level for the adult placebo-controlled trials population, i.e. the following baseline covariates and treatment-dependent covariates all have a significant effect on the risk of having a possibly suicide-related event, irrespective of treatment group. When treatment effect was added to the final model below, it did not have a significant effect.

Table 3.2 Statistically significant baseline covariates and treatment-dependent covariates for possibly suicide-related adverse events Adult placebo-controlled trials

Covariate	Odds Ratio Descriptor	Odds Ratio (95% CI)	P-value
Age	Per year increase	0.95 (0.93, 0.96)	<0.001
Indication	Depression:Other*	8.72 (5.29, 14.37)	<0.001
Formulation	CR:IR CR&IR:IR	0.23 (0.10, 0.53) 0.30 (0.13, 0.69)	<0.001 0.005
Psychiatric History	Absent:Present	0.14 (0.04, 0.47)	0.001
Psychotropic Medication	No:Yes	0.29 (0.19, 0.42)	<0.001
Baseline Suicidal Ideation	Absent:Present	0.29 (0.19, 0.44)	<0.001
Baseline Agitation	Absent:Present	2.38 (1.28, 4.41)	0.006
Early Emergent Agitation	Absent:Present	5.45 (1.33, 22.35)	0.019
Treatment	Paroxetine:Placebo	0.88 (0.60, 1.27)	0.486

* includes GAD, OCD, PMDD, PTSD, Panic and SAD
Data Source: Appendix 3, Statistical Appendix

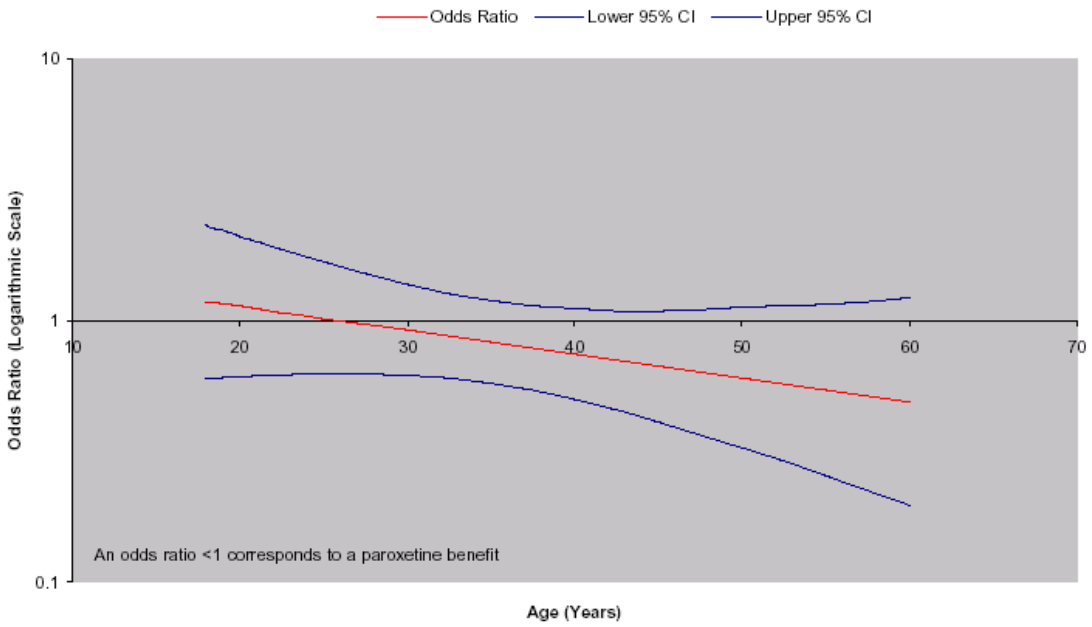
There were no statistically significant treatment by covariate interactions, i.e. for all eight of the baseline covariates and treatment-dependent covariates that were found to have a statistically significant effect on the risk of having a possibly suicide-related event, the effect was independent of treatment.

Although there were no statistically significant treatment by covariate interactions, the most significant were treatment with age (P=0.26) and treatment with baseline suicidal ideation (P=0.13) and so these two covariates will be discussed in more detail in the following paragraphs. Further discussion on the effect of dose is also warranted and is therefore presented in the following paragraphs.

Treatment with age

Figure 3.1 shows the odds ratio (paroxetine relative to placebo) and the 95% confidence interval for possibly suicide-related adverse events by age.

Figure 3.1 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)



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

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 3.3 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

Data Source: Appendix 3, Table 3.01

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 incidence of possibly suicide-related events occurring in the "on-therapy plus 30 days period" 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 3.4 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Age Group
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy**

Age Group	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	92/8481 (1.1%)	63/5808 (1.1%)	1.00 (0.72, 1.38)	1.00
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	42/1727 (2.4%)	18/1204 (1.5%)	1.64 (0.94, 2.87)	0.085
30-39 years	25/2550 (1.0%)	22/1728 (1.3%)	0.77 (0.43, 1.37)	0.37
40-49 years	20/2270 (0.9%)	14/1515 (0.9%)	0.95 (0.48, 1.89)	1.00
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

Data Source: Appendix 3, Table 3.02

Overall in the "on-therapy plus 30 days post-therapy" population there was no difference in the incidence of possibly suicide-related events between treatment groups (paroxetine 92/8481 (1.1%), placebo 63/5808 (1.1%), OR 1.00, 95% CI 0.72, 1.38, P=1.00). Forty two (42) of the 92 (46%) events in the paroxetine group and 18 of the 63 (29%) events in the placebo group occurred in the 18-29 years age group. Although there was a greater incidence of possibly suicide-related events in the paroxetine treatment group in the 18-29 year age group compared to the placebo group, this difference was not statistically significant (paroxetine 42/1727 (2.4%), placebo 18/1204 (1.5%), OR 1.64, 95% CI 0.94, 2.87, P=0.085). The incidence of possibly suicide-related events in the 50-59 years age group in the "on-therapy plus 30 days post-therapy" population was the same as in the "on therapy" population.

Treatment with baseline suicidal ideation

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

**Table 3.5 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Baseline Suicidal Ideation
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase)**

Baseline Suicidal Ideation	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
Absent*	51/8037 (0.6%)	34/5517 (0.6%)	1.03 (0.67, 1.59)	0.91
Present	15/444 (3.4%)	21/291 (7.2%)	0.45 (0.23, 0.89)	0.023

Data Source: Appendix 3, Table 3.25

* Absent includes cases where baseline suicidal ideation was not assessed.

Overall the incidence of on-therapy possibly suicide-related events was 0.8% in the paroxetine treatment group and 0.9% in the placebo group. Fifty one (51) of the 66 (77%) events in the paroxetine group and 34 of the 55 (62%) events in the placebo group occurred in patients with no baseline suicidal ideation or where baseline suicidal ideation was not assessed. However, in this sub-group, there was no difference in the incidence of possibly suicide-related events between treatment groups (paroxetine 51/8037 (0.6%), placebo 34/5517 (0.6%), OR 1.03, 95% CI 0.67, 1.59, P=0.91). In the sub-group of patients who did have baseline suicidal ideation, there was a lower incidence of possibly suicide-related events in patients in the paroxetine treatment group compared to the placebo group and this difference between treatment groups was statistically significant (paroxetine 15/444 (3.4%), placebo 21/291 (7.2%), OR 0.45, 95% CI 0.23, 0.89, P=0.023).

Effect of dose

When assessing the effect of dose alone in the adult placebo-controlled fixed-dose depression studies, dose was found to be statistically significant (P<0.001). The following table shows the incidence of possibly suicide-related events by dose in the adult placebo-controlled depression studies, including and excluding Study 057 , in which the study population comprised suicidal patients.

Table 3.6 Incidence of Possibly Suicide-Related Adverse Events by Dose Adult Placebo-Controlled Depression Trials, Including and Excluding Study 057

Dose Group	Depression Studies n/N (%)	Depression Studies Excluding Study 057 n/N (%)
Placebo	35/568 (6.2%)	6/432 (1.4%)
10mg	3/355 (0.8%)	3/355 (0.8%)
20mg	9/377 (2.4%)	9/377 (2.4%)
30mg	1/150 (0.7%)	1/150 (0.7%)
40mg	27/237 (11.4%)	0/106 (0.0%)
50mg	0/57 (0.0%)	0/57 (0.0%)

Data Source: Appendix 3, Tables 3.31 and 3.31a

In the depression studies, the apparently higher incidence of possibly suicide-related events with a 40mg dose of paroxetine compared to placebo can be explained by the results of Study 057. This study compared a dose of 40mg paroxetine against placebo and accounted for all 27 events seen with the 40mg paroxetine dose. The results of Study 057 itself showed no difference in the incidence of on-therapy possibly suicide-related events in the paroxetine treatment group compared to the placebo group (Data Source: Appendix 2B, Table 2.01a; paroxetine 27/131 (20.6%), placebo 29/136 (21.3%), OR 0.96, 95% CI 0.53, 1.73, P=1.00). The statistical modelling of the dose effect was repeated without Study 057 and showed no statistically significant association with dose (P=0.08). Taken together with the results presented in Table 3.6 this provides strong

evidence of no link between possibly suicide-related events and increasing doses of paroxetine.

3.2.2.2. Adult active-controlled trials

The following baseline covariates (Table 3.7) were statistically significant at the 5% level for the adult active-controlled trials population, i.e. each had a significant effect on the risk of having a possibly suicide-related event, irrespective of whether patients were treated with paroxetine or active comparator. When treatment effect was added to the base model, it was not significant at the 5% level (P=0.075) but the direction of the effect was in favour of paroxetine over active controls.

Table 3.7 Statistically significant baseline covariates for possibly suicide-related adverse events
Adult active-controlled trials

Covariate	Odds Ratio Descriptor	Odds Ratio (95% CI)	P-value
Age	Per year increase	0.98 (0.97, 0.99)	0.004
Disease Severity	Normal/Missing:Severe	1.14 (0.66, 1.98)	0.633
	Moderate:Severe	0.50 (0.31, 0.81)	0.004
Psychotropic Medication	No:Yes	0.61 (0.40, 0.91)	0.016
Control Medication Class	Tetracyclic:SSRI	0.35 (0.15, 0.83)	0.018
	Tricyclic:SSRI	0.52 (0.33, 0.82)	0.005
	Other*:SSRI	0.33 (0.15, 0.73)	0.006
Baseline Suicidal Ideation	Absent:Present	0.46 (0.30, 0.71)	<0.001
Treatment	Paroxetine:Comparator	0.71 (0.49, 1.03)	0.075

* includes benzodiazepines and a study involving both nortriptyline and fluoxetine
Data Source: Appendix 3, Statistical Appendix

For age, the odds ratio of 0.98 indicates that, in the active-controlled trials population, for each additional year of age, the odds of a possibly suicide-related event are 0.98 times less likely. For disease severity, the odds of a possibly suicide-related event in patients rated as "severe" were two times greater than in patients whose disease severity was rated as "moderate". Similarly, prior use of psychotropic medication, use of an SSRI as the active comparator and baseline suicidal ideation were all factors associated with an increased risk of a possibly suicide-related event.

The following baseline covariates and treatment-dependent covariates were statistically significant at the 5% level for the adult active-controlled trials population (Table 3.8). When treatment effect was added to the final model below, it was not significant at the 5% level (P=0.068) but the direction of the effect was in favour of paroxetine over active controls.

Table 3.8 Statistically significant baseline covariates and treatment-dependent covariates for possibly suicide-related adverse events Adult active-controlled trials

Covariate	Odds Ratio Descriptor	Odds Ratio (95% CI)	P-value
Age	Per year increase	0.98 (0.97, 0.99)	0.005
Disease Severity	Normal/Missing:Severe Moderate:Severe	1.14 (0.66, 1.97) 0.50 (0.31, 0.80)	0.635 0.004
Psychotropic Medication	No:Yes	0.62 (0.42, 0.94)	0.023
Control Medication Class	Tetracyclic:SSRI Tricyclic:SSRI Other*:SSRI	0.34 (0.14, 0.82) 0.53 (0.33, 0.83) 0.34 (0.15, 0.75)	0.016 0.006 0.007
Baseline Suicidal Ideation	Absent:Present	0.45 (0.29, 0.70)	<0.001
On-therapy Agitation AE	Absent:Present	0.32 (0.16, 0.61)	<0.001
Treatment	Paroxetine:Comparator	0.71 (0.49, 1.03)	0.068

* includes benzodiazepines and a study involving both nortriptyline and fluoxetine
Data Source: Appendix 3, Statistical Appendix

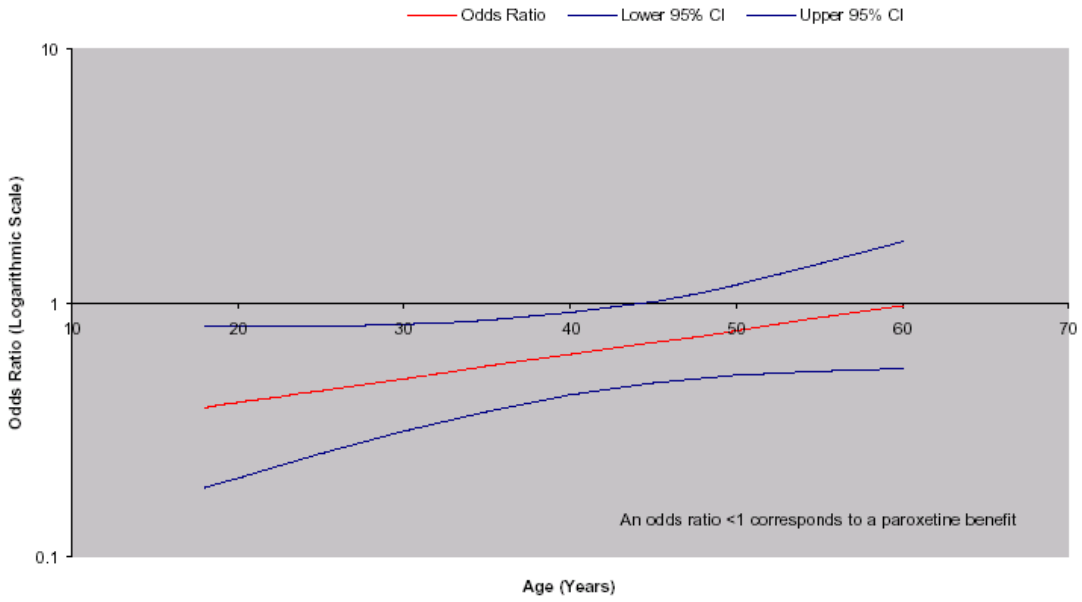
There were some differences in the significant risk factors seen in the adult active-controlled trials compared to the placebo-controlled trials population, e.g. disease severity was a significant risk factor in the active-controlled trials but not in the placebo-controlled trials and baseline agitation was a significant risk factor in the placebo-controlled trials but not in the active-controlled trials. A difference between the two populations is also seen with agitation. In the active-controlled trials population, patients with an on-therapy adverse event of agitation were at increased risk of a possibly suicide-related event, whereas in the placebo-controlled population, there was an increased risk in patients who did not have early emergent agitation.

The most significant treatment by covariate interaction (P=0.08) was with age, and this showed the benefit of treatment with paroxetine compared to active controls was highest among younger patients. Of the remaining covariates the next most significant treatment by covariate interaction (P=0.23) was with disease severity.

Treatment with age

Figure 3.2 shows the odds ratio (paroxetine relative to active comparator) and the 95% confidence interval for possibly suicide-related adverse events by age.

**Figure 3.2 Odds Ratio (Paroxetine Relative to Active Comparator) and 95% CI for Possibly Suicide-Related Adverse Events by Age
Adult Active Controlled Trials
On-Therapy (including Taper Phase)**



The odds ratio indicates 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 3.9 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Age Group
Adult Active Controlled Trials
On-Therapy (including Taper Phase)

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%)		

Data Source: Appendix 3, Table 3.07

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).

The incidence of possibly suicide-related events occurring in the "on-therapy plus 30 days period" 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 3.10 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Age Group
Adult Active Controlled Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy**

Age Group	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	79/6522 (1.2%)	76/4969 (1.5%)	0.79 (0.57, 1.08)	0.17
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	19/969 (2.0%)	22/779 (2.8%)	0.69 (0.37, 1.28)	0.27
30-39 years	19/1544 (1.2%)	15/1146 (1.3%)	0.94 (0.48, 1.86)	0.86
40-49 years	16/1647 (1.0%)	16/1182 (1.4%)	0.71 (0.36, 1.44)	0.37
50-59 years	14/1038 (1.3%)	15/835 (1.8%)	0.75 (0.36, 1.56)	0.46
60-69 years	7/831 (0.8%)	6/626 (1.0%)	0.88 (0.29, 2.63)	1.00
70+ years	4/457 (0.9%)	2/390 (0.5%)	1.71 (0.31, 9.40)	0.69
Unknown	0/32 (0.0%)	0/5 (0.0%)		

Data Source: Appendix 3, Table 3.08

No difference in the incidence of possibly suicide-related events between the paroxetine treatment group and the active comparator treatment group was seen overall or within any of the individual age groups.

Treatment with baseline suicidal ideation

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

**Table 3.11 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Baseline Suicidal Ideation
Adult Active Controlled Trials
On-Therapy (including Taper Phase)**

Baseline Suicidal Ideation	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
Absent*	41/5787 (0.7%)	48/4387 (1.1%)	0.65 (0.42, 0.98)	0.041
Present	14/735 (1.9%)	15/582 (2.6%)	0.73 (0.35, 1.53)	0.45

Data Source: Appendix 3, Table 3.38
* Absent includes cases where baseline suicidal ideation was not assessed.

Overall 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. Forty one (41) of the 55 (75%) events in the paroxetine group and 48 of the 63 (76%) events in the active comparator group occurred in patients with no baseline suicidal ideation or in cases where baseline suicidal ideation was not assessed. In this sub-group, there was a lower

incidence of possibly suicide-related events in patients in the paroxetine treatment group compared to the active comparator group and this difference between treatment groups was statistically significant (OR 0.65, 95% CI 0.42, 0.98, P=0.041). There was no significant difference in the incidence of possibly suicide-related events between treatment groups in the sub-group of patients who did have baseline suicidal ideation (OR 0.73, 95% CI 0.35, 1.53, P=0.45).

3.2.2.3. Paediatric placebo-controlled trials

The following baseline covariates were statistically significant at the 5% level for the paediatric placebo-controlled trials population, i.e. each had a significant effect on the risk of having a possibly suicide-related event, irrespective of whether patients were treated with paroxetine or placebo. When treatment effect was added to the base model, the effect was not significant at the 5% level (P=0.097) but the direction of the effect showed a higher reporting of these events among the paroxetine treated patients than among those in the placebo group.

Table 3.12 Statistically significant baseline covariates for possibly suicide-related adverse events
Paediatric placebo-controlled trials

Covariate	Odds Ratio Descriptor	Odds Ratio (95% CI)	P-value
Gender	Female:Male	3.74 (1.26, 11.14)	0.018
Disease Severity	Normal/Missing:Severe Moderate:Severe	1.24 (0.48, 3.20) 0.28 (0.10, 0.83)	0.663 0.021
Baseline Suicidal Ideation	Absent:Present	0.15 (0.06, 0.36)	<0.001
Treatment	Paroxetine:Placebo	2.14 (0.87, 5.28)	0.097

Data Source: Appendix 3, Statistical Appendix

Being female, having "severe" disease severity opposed to "moderate" disease severity, and baseline suicidal ideation all had an increased risk of a possibly suicide-related event in the paediatric placebo-controlled trials population, irrespective of whether patients were treated with paroxetine or placebo.

None of the treatment-dependent covariates were statistically significant at the 5% level. The most significant treatment by covariate interaction (P=0.06) was the treatment by baseline disease severity effect; the greatest difference between paroxetine and placebo was seen in patients where the disease at baseline was assessed as "severe", and also where baseline disease severity was unknown (almost all of the patients with unknown baseline disease severity came from Study 329, in which disease severity was not assessed at baseline) (Data Source: Appendix 3, Table 3.46). The next most significant interaction was treatment by baseline suicidal ideation (P=0.50).

Treatment with age

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. 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 3.13 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

Data Source: Appendix 3, Table 3.13a

Overall (i.e. across the defined age groups), the incidence of on-therapy possibly suicide-related events was 2.4% in the paroxetine treatment group and 1.1% in the placebo group although this difference was not statistically significant (OR 2.29, 95% CI 0.95, 5.51, P=0.069). No possibly suicide-related events were seen in the under 12 year age group in either of the treatment groups. 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 incidence of possibly suicide-related events occurring in the "on-therapy plus 30 days period" 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 3.14 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Age Group
Paediatric Placebo Controlled Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy

Age Group	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	25/738 (3.4%)	8/647 (1.2%)	2.80 (1.25, 6.25)	0.012
<12 years	1/205 (0.5%)	0/194 (0.0%)		1.00
12-15 years	13/329 (4.0%)	6/269 (2.2%)	1.80 (0.68, 4.81)	0.25
≥16 years	11/204 (5.4%)	2/184 (1.1%)	5.19 (1.13, 23.72)	0.022

Data Source: Appendix 3, Table 3.14a

Overall (i.e. across the defined age groups), the incidence of on-therapy possibly suicide-related events was 3.4% in the paroxetine treatment group and 1.2% in the placebo group and this difference was statistically significant (OR 2.80, 95% CI 1.25, 6.25, P=0.012). In the ≥16 year age group, there was a statistically significant difference between the treatment groups in the incidence of possibly suicide-related events (paroxetine 5.4%, placebo 1.1%, OR 5.19, 95% CI 1.13, 23.72, P=0.022).

Treatment with baseline suicidal ideation

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

Table 3.15 Incidence of Possibly Suicide-Related Adverse Events by Treatment Group and Baseline Suicidal Ideation Paediatric Placebo Controlled Trials On-Therapy (including Taper Phase)

Baseline Suicidal Ideation	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
Absent*	12/680 (1.8%)	4/615 (0.7%)	2.74 (0.88, 8.55)	0.081
Present	6/58 (10.3%)	3/32 (9.4%)	1.12 (0.26, 4.80)	1.00

Data Source: Appendix 3, Table 3.49
* Absent includes cases where baseline suicidal ideation was not assessed.

In patients with baseline suicidal ideation, there was no statistically significant difference in the incidence of possibly suicide-related events between treatment groups. Higher incidence rates were seen in patients with baseline suicidal ideation than in patients where baseline suicidal ideation was classed as "absent". However, the data for the cases where baseline suicidal ideation was classed as "absent" includes studies where suicidal ideation (as per the definition outlined in Section 3.2.1) was not assessed and so does not provide a solid assessment of the incidence of possibly suicide-related events in paediatric patients without baseline suicidal ideation.

3.2.3. Risk factors of self-harm

3.2.3.1. Adult placebo-controlled trials

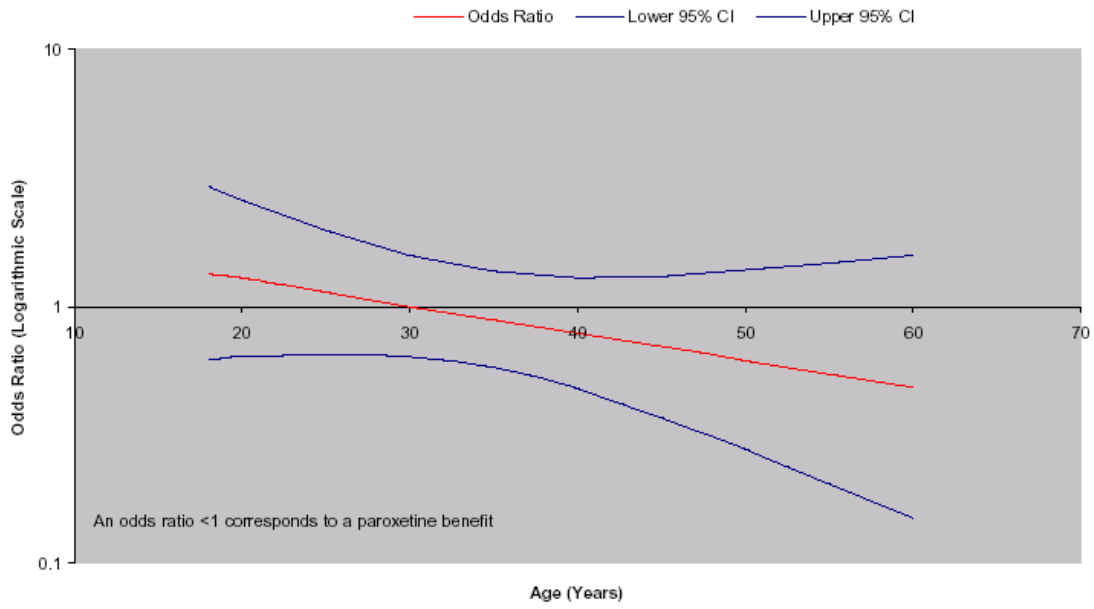
The base model for self-harm in the adult placebo-controlled trials included the same covariates as previously described for the possibly suicide-related events. As for the possibly suicide-related events, the treatment effect was not significant.

When assessing treatment-dependent effects, early emergent agitation was found to have a significant effect which was consistent with the model for possibly suicide-related events. One treatment by covariate interaction was found to be significant and that was treatment by baseline suicidal ideation (P<0.01).

Treatment with age

Figure 3.3 shows the odds ratio (paroxetine relative to placebo) and the 95% confidence interval for self harm events by age.

**Figure 3.3 Odds Ratio (Paroxetine Relative to Placebo) and 95% CI for Self Harm Events by Age
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase)**



Below the age of 30 years, the odds ratio indicates that there is a slightly greater risk of having self harm events on paroxetine than on placebo in the adult placebo-controlled trials, but this was not statistically significant. Above the age of 30 years, there was a reduced risk of having self harm events on paroxetine than on placebo but again this was not statistically significant.

The incidence of on-therapy self harm 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 3.16 Incidence of Self Harm 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	51/8481 (0.6%)	38/5808 (0.7%)	0.92 (0.60, 1.40)	0.75
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	27/1727 (1.6%)	12/1204 (1.0%)	1.58 (0.80, 3.13)	0.25
30-39 years	12/2550 (0.5%)	15/1728 (0.9%)	0.54 (0.25, 1.16)	0.12
40-49 years	9/2270 (0.4%)	8/1515 (0.5%)	0.75 (0.29, 1.95)	0.62
50-59 years	2/1152 (0.2%)	3/807 (0.4%)	0.47 (0.08, 2.80)	0.41
60-69 years	0/530 (0.0%)	0/381 (0.0%)		
70+ years	1/247 (0.4%)	0/172 (0.0%)		1.00

Data Source: Appendix 3, Table 3.03

In all of the age groups, there was no statistically significant difference between the paroxetine treatment group and the placebo group in the incidence of self harm events.

The incidence of self harm events occurring in the "on-therapy plus 30 days period" 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 3.17 Incidence of Self Harm Events by Treatment Group and Age Group Adult Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Age Group	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	63/8481 (0.7%)	41/5808 (0.7%)	1.05 (0.71, 1.56)	0.84
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	33/1727 (1.9%)	12/1204 (1.0%)	1.94 (1.00, 3.76)	0.048
30-39 years	15/2550 (0.6%)	17/1728 (1.0%)	0.60 (0.30, 1.20)	0.15
40-49 years	12/2270 (0.5%)	9/1515 (0.6%)	0.89 (0.37, 2.12)	0.83
50-59 years	2/1152 (0.2%)	3/807 (0.4%)	0.47 (0.08, 2.80)	0.41
60-69 years	0/530 (0.0%)	0/381 (0.0%)		
70+ years	1/247 (0.4%)	0/172 (0.0%)		1.00

Data Source: Appendix 3, Table 3.04

There were no statistically significant differences between the paroxetine treatment group and the placebo group in the incidence of self harm events in any of the age groups, with the exception of the 18-29 year group, where there was a greater incidence of self harm events in the paroxetine group compared to the placebo group (paroxetine 1.9%, placebo 1.0%, OR 1.94, 95% CI 1.00, 3.76, P=0.048).

Treatment with baseline suicidal ideation

The incidence of on-therapy self harm events by treatment group and baseline suicidal ideation is summarised in the following table. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test.

Table 3.18 Incidence of Self Harm Events by Treatment Group and Baseline Suicidal Ideation
Adult Placebo Controlled Trials
On-Therapy (including Taper Phase)

Baseline Suicidal Ideation	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	51/8481 (0.6%)	38/5808 (0.7%)	0.92 (0.60, 1.40)	0.75
Absent*	40/8037 (0.5%)	20/5517 (0.4%)	1.37 (0.80, 2.35)	0.29
Present	11/444 (2.5%)	18/291 (6.2%)	0.39 (0.18, 0.83)	0.019

Data Source: Appendix 3, Table 3.73
* Absent includes cases where baseline suicidal ideation was not assessed.

Overall the incidence of on-therapy self harm events was 0.6% in the paroxetine treatment group and 0.7% in the placebo group. Forty (40) of the 51 (78%) events in the paroxetine group and 20 of the 38 (53%) events in the placebo group occurred in patients with no baseline suicidal ideation or where baseline suicidal ideation was not assessed. However, in this sub-group, there was no difference in the incidence of self harm events between treatment groups (paroxetine 40/8037 (0.5%), placebo 20/5517 (0.4%), OR 1.37, 95% CI 0.80, 2.35, P=0.29). In the sub-group of patients who did have baseline suicidal ideation, there was a lower incidence of self harm events in patients in the paroxetine treatment group compared to the placebo group and this difference between treatment groups was statistically significant (paroxetine 11/444 (2.5%), placebo 18/291 (6.2%), OR 0.39, 95% CI 0.18, 0.83, P=0.019).

3.2.3.2. Adult active-controlled trials

For adult active control trials, the base model for self harm included the same covariates as the model for possibly suicide-related events, except for control medication which was not significant at the 5% level (P=0.086) for the analysis of self harm events and therefore was not included in the base model. Treatment effect was not significant. When assessing treatment emergent events, treatment emergent agitation had an effect consistent with the model for possibly suicide-related events. No treatment by covariate interactions were found to be significant, although treatment by age approached significance (P=0.074), consistent with findings for possibly suicide-related events.

Treatment with age

Figure 3.4 shows the odds ratio (paroxetine relative to placebo) and the 95% confidence interval for self harm events by age.

Figure 3.4 Odds Ratio (Paroxetine Relative to Placebo) and 95% CI for Self Harm Events by Age
Adult Active Controlled Trials
On-Therapy (including Taper Phase)

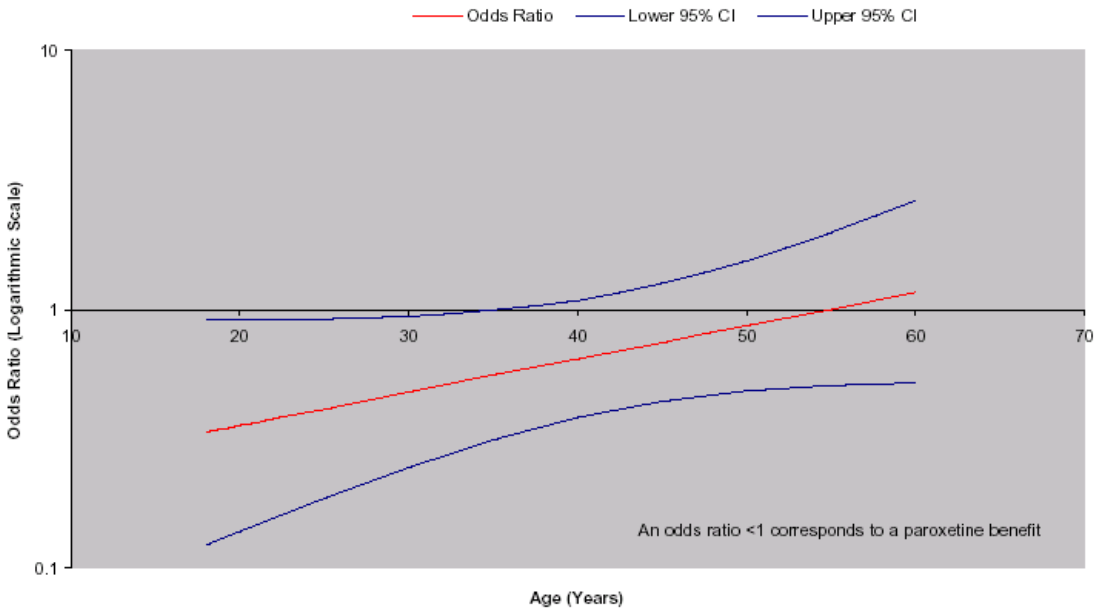


Figure 3.4 shows a similar pattern to that seen for possibly suicide-related events in the active-controlled studies (see Figure 3.2), with paroxetine showing a statistically significant benefit over the active control up until around the mid-30 year mark.

The incidence of on-therapy self harm 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 3.19 Incidence of Self Harm Events by Treatment Group and Age Group
Adult Active Controlled Trials
On-Therapy (including Taper Phase)

Age Group	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	29/6522 (0.4%)	32/4969 (0.6%)	0.69 (0.42, 1.14)	0.16
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	6/969 (0.6%)	12/779 (1.5%)	0.40 (0.15, 1.07)	0.092
30-39 years	7/1544 (0.5%)	4/1146 (0.3%)	1.30 (0.38, 4.45)	0.77
40-49 years	5/1647 (0.3%)	6/1182 (0.5%)	0.60 (0.18, 1.96)	0.54
50-59 years	3/1038 (0.3%)	7/835 (0.8%)	0.34 (0.09, 1.33)	0.12
60-69 years	5/831 (0.6%)	3/626 (0.5%)	1.26 (0.30, 5.28)	1.00
70+ years	3/457 (0.7%)	0/390 (0.0%)		0.25
Unknown	0/32 (0.0%)	0/5 (0.0%)		

Data Source: Appendix 3, Table 3.09

There were no statistically significant differences between the paroxetine treatment group and the active comparator group in the incidence of on-therapy self harm events in any of the age groups.

The incidence of self harm events occurring in the "on-therapy plus 30 days period" 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 3.20 Incidence of Self Harm Events by Treatment Group and Age Group
Adult Active Controlled Trials
On-Therapy (including Taper Phase) plus 30 days post-therapy

Age Group	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	42/6522 (0.6%)	42/4969 (0.8%)	0.76 (0.49, 1.17)	0.22
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	11/969 (1.1%)	13/779 (1.7%)	0.68 (0.30, 1.52)	0.41
30-39 years	9/1544 (0.6%)	7/1146 (0.6%)	0.95 (0.35, 2.57)	1.00
40-49 years	7/1647 (0.4%)	9/1182 (0.8%)	0.56 (0.21, 1.50)	0.31
50-59 years	7/1038 (0.7%)	8/835 (1.0%)	0.70 (0.25, 1.94)	0.60
60-69 years	5/831 (0.6%)	4/626 (0.6%)	0.94 (0.25, 3.52)	1.00
70+ years	3/457 (0.7%)	1/390 (0.3%)	2.57 (0.27, 24.81)	0.63
Unknown	0/32 (0.0%)	0/5 (0.0%)		

Data Source: Appendix 3, Table 3.10

In the on-therapy plus 30 days post-therapy population, there were no statistically significant differences between the paroxetine treatment group and the active comparator group in the incidence of self harm events in any of the age groups.

Treatment with baseline suicidal ideation

The incidence of on-therapy self harm events by treatment group and baseline suicidal ideation is summarised in the following table. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test.

Table 3.21 Incidence of Self Harm Events by Treatment Group and Baseline Suicidal Ideation
Adult Active Controlled Trials
On-Therapy (including Taper Phase)

Baseline Suicidal Ideation	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	29/6522 (0.4%)	32/4969 (0.6%)	0.69 (0.42, 1.14)	0.16
Absent*	22/5787 (0.4%)	23/4387 (0.5%)	0.72 (0.40, 1.30)	0.29
Present	7/735 (1.0%)	9/582 (1.5%)	0.61 (0.23, 1.65)	0.45

Data Source: Appendix 3, Table 3.74
* Absent includes cases where baseline suicidal ideation was not assessed.

Overall the incidence of on-therapy self harm events was 0.4% in the paroxetine treatment group and 0.6% in the active comparator group. In both sub-groups (i.e. patients with baseline suicidal ideation and patients with no baseline suicidal ideation or where baseline suicidal ideation was not assessed), there was no statistically significant difference between the paroxetine treatment group and the active comparator group in terms of the incidence of self harm events.

3.2.3.3. Paediatric placebo-controlled trials

For the paediatric placebo-controlled population, the base model for self harm events included treatment, indication, baseline suicidal ideation and gender, whereas the model for possibly suicide-related events had included disease severity, baseline suicidal ideation and gender. There was no significant treatment effect. When assessing treatment dependent events, a significant effect was found for the event of on-therapy hostility (P=0.048), although this appeared to be driven by just one patient in the paroxetine treatment group with a treatment emergent hostility event and a subsequent self-harm event. There were no significant treatment by covariate interactions, i.e. any effects were independent of treatment.

Treatment with age

The incidence of on-therapy self harm 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 3.22 Incidence of Self Harm 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	15/738 (2.0%)	5/647 (0.8%)	2.66 (0.96, 7.37)	0.069
<12 years	0/205 (0.0%)	0/194 (0.0%)		
12-15 years	7/329 (2.1%)	4/269 (1.5%)	1.44 (0.42, 4.97)	0.76
≥16 years	8/204 (3.9%)	1/184 (0.5%)	7.47 (0.93, 60.31)	0.039

Data Source: Appendix 3, Table 3.15a

Overall (i.e. across the defined age groups), the incidence of on-therapy self harm events was 2.0% in the paroxetine treatment group and 0.8% in the placebo group although this difference was not statistically significant (OR 2.66, 95% CI 0.96, 7.37, P=0.069). In the ≥16 year age group, there was a statistically significant difference between the treatment groups in the incidence of self harm events (paroxetine 3.9%, placebo 0.5%, OR 7.47, 95% CI 0.93, 60.31, P=0.039).

The incidence of self harm events occurring in the "on-therapy plus 30 days period" 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 3.23 Incidence of Self Harm Events by Treatment Group and Age Group Paediatric Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Age Group	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	18/738 (2.4%)	5/647 (0.8%)	3.21 (1.19, 8.70)	0.019
<12 years	0/205 (0.0%)	0/194 (0.0%)		
12-15 years	9/329 (2.7%)	4/269 (1.5%)	1.86 (0.57, 6.12)	0.40
≥16 years	9/204 (4.4%)	1/184 (0.5%)	8.45 (1.06, 67.33)	0.022

Data Source: Appendix 3, Table 3.16a

Overall (i.e. across the defined age groups), the incidence of self harm events in the "on therapy plus 30 days" period was 2.4% in the paroxetine treatment group and 0.8% in the placebo group and this difference was statistically significant (OR 3.21, 95% CI 1.19, 8.70, P=0.019). In the ≥16 year age group, there was a statistically significant difference between the treatment groups in the incidence of self harm events (paroxetine 4.4%, placebo 0.5%, OR 8.45, 95% CI 1.06, 67.33, P=0.022).

Treatment with baseline suicidal ideation

The incidence of on-therapy self harm events by treatment group and baseline suicidal ideation is summarised in the following table. Comparisons of the incidence of events between treatment groups were made using Fisher's exact test.

Table 3.24 Incidence of Self Harm Events by Treatment Group and Baseline Suicidal Ideation Paediatric Placebo Controlled Trials On-Therapy (including Taper Phase)

Baseline Suicidal Ideation	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	15/738 (2.0%)	5/647 (0.8%)	2.66 (0.96, 7.37)	0.069
Absent*	9/680 (1.3%)	3/615 (0.5%)	2.74 (0.74, 10.15)	0.15
Present	6/58 (10.3%)	2/32 (6.3%)	1.73 (0.33, 9.12)	0.71

Data Source: Appendix 3, Table 3.75

* Absent includes cases where baseline suicidal ideation was not assessed.

Overall the incidence of on-therapy self harm events was 2.0% in the paroxetine treatment group and 0.8% in the placebo group, but this difference was not statistically significant (OR 2.66, 95% CI 0.96, 7.37, P=0.069). In both sub-groups (i.e. patients with baseline suicidal ideation and patients with no baseline suicidal ideation or where

baseline suicidal ideation was not assessed), there was a higher incidence of self harm events in the paroxetine treatment group than in the placebo group but the differences were not statistically significant.

3.2.4. Risk factors of hostility

3.2.4.1. Adult placebo-controlled trials

The following baseline covariates were statistically significant at the 5% level for the adult placebo-controlled trials population, i.e. each had a significant effect on the risk of having a hostility event, irrespective of whether the patient was treated with paroxetine or placebo. When treatment effect was added to the base model, it did not have a significant effect.

Table 3.25 Statistically significant baseline covariates for hostility events Adult placebo-controlled trials

Covariate	Odds Ratio Descriptor	Odds Ratio (95% CI)	P-value
Indication	OCD:Other*	4.07 (1.86, 8.88)	<0.001
Age	Per year increase	0.97 (0.94, 1.00)	0.022
Treatment	Paroxetine:Placebo	1.01 (0.54, 1.91)	0.970

* includes Depression, GAD, PMDD, PTSD, Panic and SAD
Data Source: Appendix 3, Statistical Appendix

For indication, the odds of a hostility event were approximately 4 times greater in OCD trials than in the studies conducted in other indications. In the case of age, the odds ratio of 0.97 indicates that in the placebo-controlled trials population, for each additional year of age, the odds of a hostility event are 0.97 times less likely.

There were no statistically significant treatment by covariate interactions (P>0.47).

When assessing the effect of dose alone in the adult placebo controlled fixed dose depression trials, no significant effect was seen at the 5% level (P=0.08).

Treatment with age

The incidence of on-therapy hostility 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 3.26 Incidence of Hostility 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	24/8481 (0.3%)	16/5808 (0.3%)	1.03 (0.55, 1.94)	1.00
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	8/1727 (0.5%)	7/1204 (0.6%)	0.80 (0.29, 2.20)	0.79
30-39 years	7/2550 (0.3%)	4/1728 (0.2%)	1.19 (0.35, 4.06)	1.00
40-49 years	7/2270 (0.3%)	2/1515 (0.1%)	2.34 (0.49, 11.28)	0.33
50-59 years	1/1152 (0.1%)	0/807 (0.0%)		1.00
60-69 years	1/530 (0.2%)	3/381 (0.8%)	0.24 (0.02, 2.30)	0.31
70+ years	0/247 (0.0%)	0/172 (0.0%)		

Data Source: Appendix 3, Table 3.05

There were no differences in the incidence of on-therapy hostility events between the paroxetine treatment group and the placebo group overall or within any of the individual age groups. The same was also seen for the "on-therapy plus 30 day" period, as shown in the following table.

Table 3.27 Incidence of Hostility Events by Treatment Group and Age Group Adult Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Age Group	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	32/8481 (0.4%)	16/5808 (0.3%)	1.37 (0.75, 2.50)	0.38
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	10/1727 (0.6%)	7/1204 (0.6%)	1.00 (0.38, 2.62)	1.00
30-39 years	10/2550 (0.4%)	4/1728 (0.2%)	1.70 (0.53, 5.42)	0.43
40-49 years	9/2270 (0.4%)	2/1515 (0.1%)	3.01 (0.65, 13.96)	0.22
50-59 years	2/1152 (0.2%)	0/807 (0.0%)		0.52
60-69 years	1/530 (0.2%)	3/381 (0.8%)	0.24 (0.02, 2.30)	0.31
70+ years	0/247 (0.0%)	0/172 (0.0%)		

Data Source: Appendix 3, Table 3.06

3.2.4.2. Adult active-controlled trials

The following baseline covariates were statistically significant at the 5% level for the adult active controlled trials population. When treatment effect was added to the base model, it did not have a significant effect.

Table 3.28 Statistically significant baseline covariates for hostility events Adult active controlled trials

Covariate	Odds Ratio Descriptor	Odds Ratio (95% CI)	P-value
Disease Severity	Normal/Missing:Severe	0.64 (0.16, 2.59)	0.527
	Mild/Moderate:Severe	2.19 (0.97, 4.96)	0.061
Control Medication	Benzodiazepine/Other:SSRI	1.51 (0.39, 5.87)	0.551
	Tricyclic:SSRI	0.37 (0.16, 0.85)	0.828
	Tetracyclic:SSRI	0.89 (0.32, 2.48)	0.019
Treatment	Paroxetine:Comparator	0.70 (0.36, 1.35)	0.283

Data Source: Appendix 3, Statistical Appendix

There was an increased risk of a hostility event in patients with "mild/moderate" disease severity compared to "severe" disease severity, irrespective of whether the patient was treated with paroxetine or active comparator. Reported rates of hostility varied across the different classes of active comparator. However, there were no significant differences between paroxetine and any of the active control groups.

There were no statistically significant treatment by covariate interactions (P>0.49).

Treatment with age

The incidence of on-therapy hostility 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 3.29 Incidence of Hostility Events by Treatment Group and Age Group Adult Active Controlled Trials On-Therapy (including Taper Phase)

Age Group	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	18/6522 (0.3%)	20/4969 (0.4%)	0.68 (0.36, 1.30)	0.25
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	3/969 (0.3%)	4/779 (0.5%)	0.60 (0.13, 2.70)	0.71
30-39 years	5/1544 (0.3%)	6/1146 (0.5%)	0.62 (0.19, 2.03)	0.54
40-49 years	4/1647 (0.2%)	7/1182 (0.6%)	0.41 (0.12, 1.40)	0.22
50-59 years	4/1038 (0.4%)	1/835 (0.1%)	3.23 (0.36, 28.92)	0.39
60-69 years	1/831 (0.1%)	0/626 (0.0%)		1.00
70+ years	1/457 (0.2%)	2/390 (0.5%)	0.43 (0.04, 4.71)	0.60
Unknown	0/32 (0.0%)	0/5 (0.0%)		

Data Source: Appendix 3, Table 3.11

There were no differences in the incidence of on-therapy hostility events between the paroxetine treatment group and the active comparator group overall or within any of the individual age groups. The same was also seen for the "on-therapy plus 30 day" period, as shown in the following table.

Table 3.30 Incidence of Hostility Events by Treatment Group and Age Group Adult Active Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Age Group	Paroxetine n/N (%)	Comparator n/N (%)	OR (95% CI)	P value
Overall	22/6522 (0.3%)	22/4969 (0.4%)	0.76 (0.42, 1.38)	0.37
<18 years	0/4 (0.0%)	0/6 (0.0%)		
18-29 years	4/969 (0.4%)	5/779 (0.6%)	0.64 (0.17, 2.40)	0.52
30-39 years	5/1544 (0.3%)	6/1146 (0.5%)	0.62 (0.19, 2.03)	0.54
40-49 years	7/1647 (0.4%)	8/1182 (0.7%)	0.63 (0.23, 1.73)	0.43
50-59 years	4/1038 (0.4%)	1/835 (0.1%)	3.23 (0.36, 28.92)	0.39
60-69 years	1/831 (0.1%)	0/626 (0.0%)		1.00
70+ years	1/457 (0.2%)	2/390 (0.5%)	0.43 (0.04, 4.71)	0.60
Unknown	0/32 (0.0%)	0/5 (0.0%)		

Data Source: Appendix 3, Table 3.12

3.2.4.3. Paediatric placebo-controlled trials

The following baseline covariates were statistically significant at the 5% level for the paediatric placebo controlled trials population. When treatment was added to the model, there was a statistically significant difference between paroxetine and placebo (P<0.001) with hostility events being reported at a greater incidence in paroxetine treated patients than among placebo patients.

Table 3.31 Statistically significant baseline covariates for hostility events Paediatric placebo controlled trials

Covariate	Odds Ratio Descriptor	Odds Ratio (95% CI)	P-value
Disease Severity	Missing:Severe	5.12 (1.21, 21.70)	0.027
	Normal:Severe	0.45 (0.11, 1.79)	0.256
	Mild/Moderate:Severe	0.41 (0.17, 1.00)	0.051
Indication	Depression:OCD	0.16 (0.04, 0.62)	0.008
	SAD:OCD	0.50 (0.19, 1.36)	0.175
Age	Per year increase	0.82 (0.71, 0.95)	0.006
Treatment	Paroxetine:Placebo	7.13 (2.46, 20.69)	<0.001

Data Source: Appendix 3, Statistical Appendix

There was an increased risk of a hostility event in patients with "severe" disease severity compared to "mild/moderate" disease severity. There was also an increased risk of a hostility event in cases where baseline disease severity was unknown (almost all of the patients with unknown baseline disease severity came from Study 329, in which disease severity was not assessed at baseline) (Data Source: Appendix 3, Table 3.70). There was an increased risk of a hostility event in the OCD trials compared to the depression trials, and although this was also true of the OCD patients compared to the SAD patients this comparison was not statistically significant. In the case of age, the odds ratio of 0.82

indicates that in the paediatric population, for each additional year of age, the odds of a hostility event are 0.82 times less likely.

There were no statistically significant treatment by covariate interactions (P>0.29).

Treatment with age

The incidence of on-therapy hostility 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 3.32 Incidence of Hostility 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	27/738 (3.7%)	4/647 (0.6%)	6.10 (2.12, 17.54)	<0.001
<12 years	15/205 (7.3%)	1/194 (0.5%)	15.24 (1.99, 116.5)	<0.001
12-15 years	10/329 (3.0%)	3/269 (1.1%)	2.78 (0.76, 10.20)	0.16
≥16 years	2/204 (1.0%)	0/184 (0.0%)		0.50

Data Source: Appendix 3, Table 3.17a

There was a statistically significant greater incidence of hostility events in the paroxetine treatment group compared to the placebo group overall and in the <12 year age group. In the 12-15 year age group, there was a greater incidence of hostility events in the paroxetine group compared to the placebo group although the difference was not statistically significant. There was no statistically significant difference in the incidence of a hostility event in the ≥16 years age group.

The incidence of hostility events occurring in the "on-therapy plus 30 days period" 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 3.33 Incidence of Hostility Events by Treatment Group and Age Group Paediatric Placebo Controlled Trials On-Therapy (including Taper Phase) plus 30 days post-therapy

Age Group	Paroxetine n/N (%)	Placebo n/N (%)	OR (95% CI)	P value
Overall	28/738 (3.8%)	4/647 (0.6%)	6.34 (2.21, 18.17)	<0.001
<12 years	15/205 (7.3%)	1/194 (0.5%)	15.24 (1.99, 116.5)	<0.001
12-15 years	11/329 (3.3%)	3/269 (1.1%)	3.07 (0.85, 11.11)	0.10
≥16 years	2/204 (1.0%)	0/184 (0.0%)		0.50

Data Source: Appendix 3, Table 3.18a

As for the on-therapy period, there was a statistically significant greater incidence of hostility events in the paroxetine treatment group compared to the placebo group overall and in the <12 year age group. In the 12-15 year age group, there was a greater incidence of hostility events in the paroxetine group compared to the placebo group although the difference was not statistically significant. There was no statistically significant difference in the incidence of a hostility event in the ≥16 years age group.

3.3. Post-marketing reports

3.3.1. Strategy of Analysis for Potential Risk Factors

To analyse the dataset of post-marketing reports of self-harm/suicidal behaviour and the separate dataset of post-marketing reports of hostility for potential risk factors, a combination of electronic searching and manual case review was utilised. Information on the age distribution, gender, indication for use of paroxetine, previous psychiatric history, concomitant pharmacotherapies, country of origin and proportion of cases received per year was obtained by electronic searching of coded database fields. In addition, a manual review of case narratives of a sub-set of the cases in the two datasets was conducted to identify the time-to-onset following initiation of paroxetine and the dose at the time of the event. Case narrative review is required to determine the time-to-onset and dosage data in patients receiving varying doses of paroxetine.

To analyse the indication for use of paroxetine, the proportion of cases which documented an indication including depression was identified. A second analysis was conducted to identify the proportion of reports which had an indication including OCD. This method was used since many reports described multiple indications for use (e.g. depression and anxiety). The MedDRA preferred terms used to define depression were:

> "Depression", "Depressed mood", "Depression suicidal", "Major depressive disorder", "Postpartum depression", "Depression postmenopausal", "Dysthymic disorder", "Bipolar disorder", "Bipolar I disorder" and "Bipolar II disorder".

These terms were identified from an output of all indications that had been reported for the entire paroxetine dataset.

Similarly, the terms used to define OCD were:

> "Obsessive-compulsive disorder", "Obsessive thoughts" and "Compulsions".

To analyse previous psychiatric history cases were identified which reported patients who had a previous history, concurrent condition or an indication for use of a concurrent drug which mapped to a specific list of MedDRA preferred terms.

For the self-harm/suicidal behaviour dataset the following terms were considered to represent relevant psychiatric history:

> "Overdose NOS", "Multiple drug overdose", "Non-accidental overdose", "Self-mutilation", "Intentional self-injury", "Self-injurous ideation", "Suicidal ideation", "Suicide attempt" or "Depression suicidal".

These terms were identified from an output of all indications for all drugs in the entire paroxetine dataset and all medical history terms in the entire paroxetine dataset.

For the hostility dataset the following terms were considered relevant:

> "Aggression", "Hostility", "Homicidal ideation", "Fight in school" or "Oppositional defiant disorder".

In addition to the above search of coded terms, the medical history narratives of the self-harm/suicidal behaviour dataset were searched for text strings containing relevant phrases such as:

> "suic", "attempt", "overdos", "self inflict".

Similarly the medical history narratives of the hostility dataset were searched for text strings including:

> "murder", "violen", "aggress" or "fight".

To analyse the use of concomitant pharmacotherapies, cases in which psychotropic medications, within the ATC groups N05 (psycholeptics) and N06 (psychoanaleptics), were coded either as historic, concomitant or co-suspect medications were identified.

A comparison of the distribution of these potential risk factors in the self-harm/suicidal behaviour and hostility datasets was made against the datasets containing all paroxetine reports minus the self-harm/suicidal behaviour or hostility dataset. This comparison was conducted separately for the paediatric datasets and then the adult plus unspecified age datasets. For example, the 126 reports of self-harm/suicidal behaviour in paediatric patients were compared to the 1,246 reports involving paediatric patients which did not describe self-harm/suicidal behaviour. Likewise, the 1,413 reports of self-harm/suicidal behaviour in adult patients were compared to the 40,059 reports involving adult patients which did not describe these events.

An exception to this method was made for the analysis of the country of origin of the reports and the proportion of the reports received per year. In these two instances, the distribution of the events of interest (self-harm/suicidal behaviour or hostility) was compared to the distribution of reports of all events.

3.3.2. Results of Analysis of Potential Risk Factors

3.3.2.1. Self-harm/suicidal behaviour - adults plus patients of unspecified age

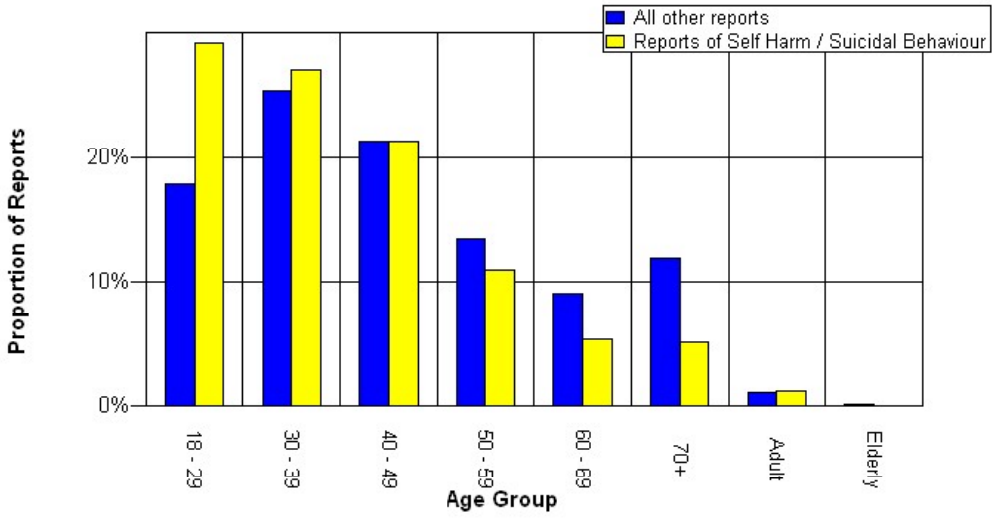
Age distribution

GSK received 1,413 reports of self-harm/suicidal behaviour in adults plus patients of unspecified age up to 31 May 2003 and this dataset is compared to 40,059 reports of "other events" in adults + patients of unspecified age received in the same period.

The age of the patient was not known in 26% (n = 368) of the cases of self-harm/suicidal behaviour, but the age distribution of the cases where an indication of the patient's age

was reported is presented in Figure 3.5. Note: the age groups "adult" and "elderly" are categories used when a specific age was not provided but when it was known from the reporter's description that the category was appropriate.

Figure 3.5 Age Distribution



The graph shows that self-harm/suicidal behaviour events were reported more frequently in young adults, with 29.2% of self-harm/suicidal events being reported in the 18-29 years age group whereas 17.9% of "other events" were reported to have occurred in the same age group.

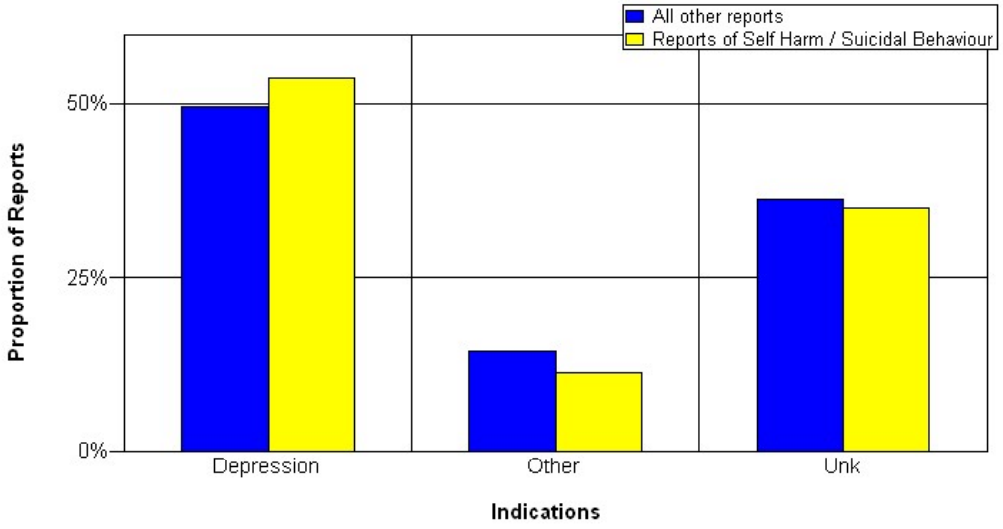
Gender

The self-harm/suicidal behaviour dataset included a greater proportion of male patients compared to the dataset of "other events", with 36.5% male (n = 516), 54.6% female (n = 772) and 8.9% unspecified gender (n = 125) compared to 26.0% male (n = 10,422), 63.0% female (n = 25,254) and 11.0% unspecified gender (n = 4,383) respectively.

Indication

The proportion of patients who were receiving paroxetine for depression (or depression plus other indications) was 54% (n = 760) in the self-harm/suicidal behaviour dataset, with 35% (n = 493) having an unknown indication and 11% (n = 160) another indication. In the "other events" dataset the proportion of patients receiving paroxetine for depression was 50% (n = 19,838), with 36 % (n = 14,476) having an unknown indication and 14% (n = 5,745) another indication, as presented in Figure 3.6.

Figure 3.6 Indication of depression

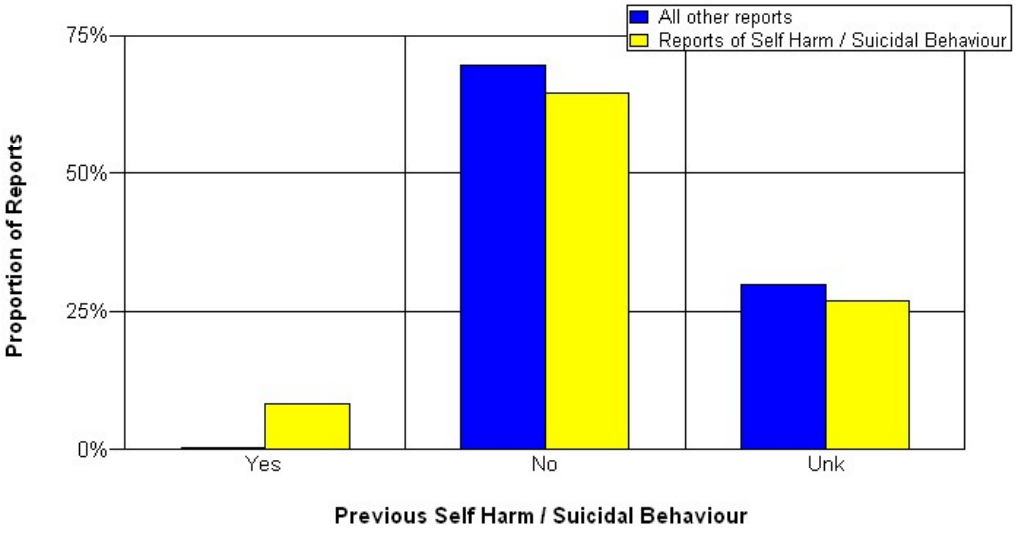


The proportion of patients who were receiving paroxetine for obsessive compulsive disorder (or OCD plus other indications) was similar in both datasets, with 1.7% (n = 24) in the self-harm/suicidal behaviour dataset and 2.5% (n = 1,013) in the "other events" dataset.

Previous psychiatric history

The proportion of patients who had experienced self-harm/suicidal behaviour prior to the use of paroxetine was higher in the self-harm/suicidal behaviour dataset than the "other events" dataset as shown in Figure 3.7.

Figure 3.7 Relevant prior history



Of the reports in the self-harm/suicidal behaviour dataset, 8.3% (n = 117) reported that the patient had experienced similar events previously (i.e. self-harm/suicidal behaviour

was reported as medical history, a concurrent condition or as an indication for a concomitant medication) as opposed to only 0.4% (n = 160) in the "other events" dataset.

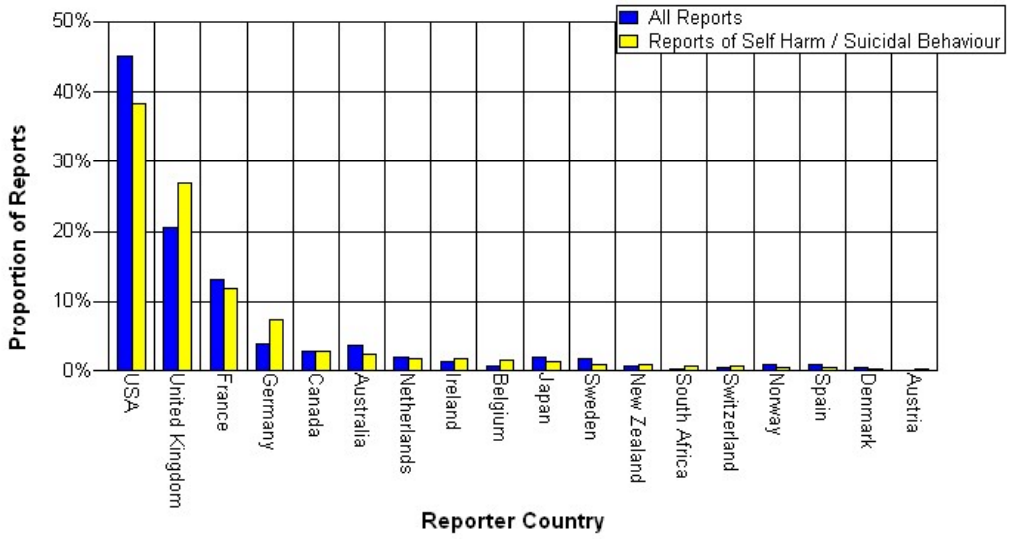
Concomitant pharmacotherapies

A notable difference was observed when comparing the proportion of patients who were receiving other psychotropic medications. In the self-harm/suicidal behaviour dataset, the proportion of patients reported to have received one or more concomitant psychotropic medications was 40.3% (n = 570) compared to 24.1% (n = 9,673) in the "other events" dataset.

Country of origin and proportion of cases received per year

The analysis of reporter country distribution allowed a comparison of the proportion of all self-harm/suicidal events with the proportion of all events which arose in that country. Figure 3.8 shows that the proportion of self-harm/suicidal behaviour events received in the UK and Germany was greater than the proportion of all events received from those countries. The graph includes those countries which reported more than one case of self-harm/suicidal behaviour.

Figure 3.8 Distribution by country

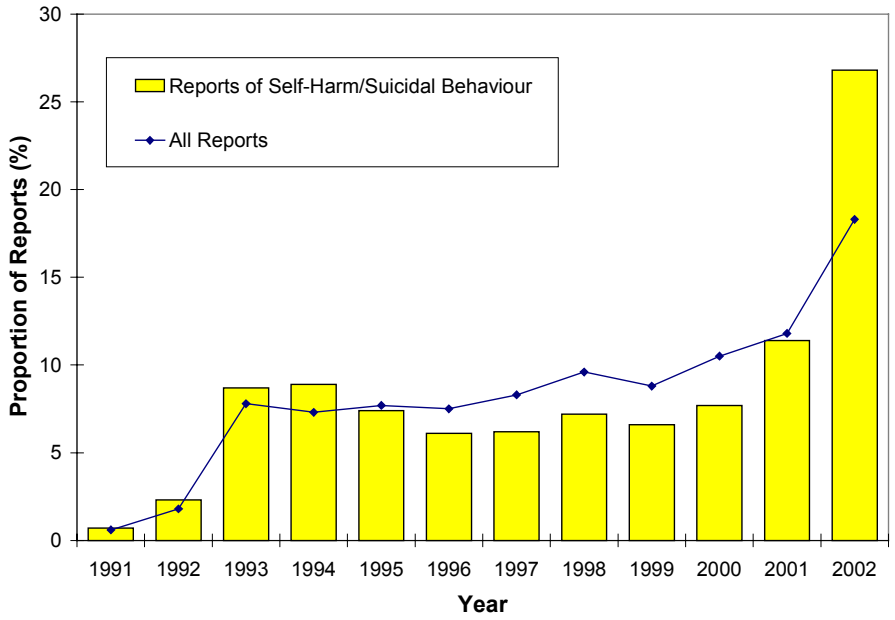


Although only 20.3% of all adverse event reports arose from the UK, 26.8% of those involving self-harm/suicidal behaviour events were reported from the UK. Germany was also the source of relatively more self-harm/suicidal behaviour events, with 7.4% (n = 105) coming from Germany although only 3.7% (n = 1562) of all reports were reported from Germany. It is believed that this is probably as a result of publicity given to these types of events in these countries, rather than being an indicator of specific race vulnerability.

To observe how the rate of reporting of self-harm/suicidal behaviour has changed over the marketed life of the product, a graph of the proportion of these reports which have been received each year since paroxetine was launched in 1991 until the end of 2002 is

provided in Figure 3.9. This figure presents the data for all self-harm/suicidal behaviour reports involving both adult and paediatric patients. The proportion of the total dataset of paroxetine adverse event reports up to the end of 2002 which were received each year is also provided so that the profile of self-harm/suicidal behaviour reporting can be compared against the overall pattern of reporting of all adverse events for paroxetine.

Figure 3.9 Proportion of reports received each year

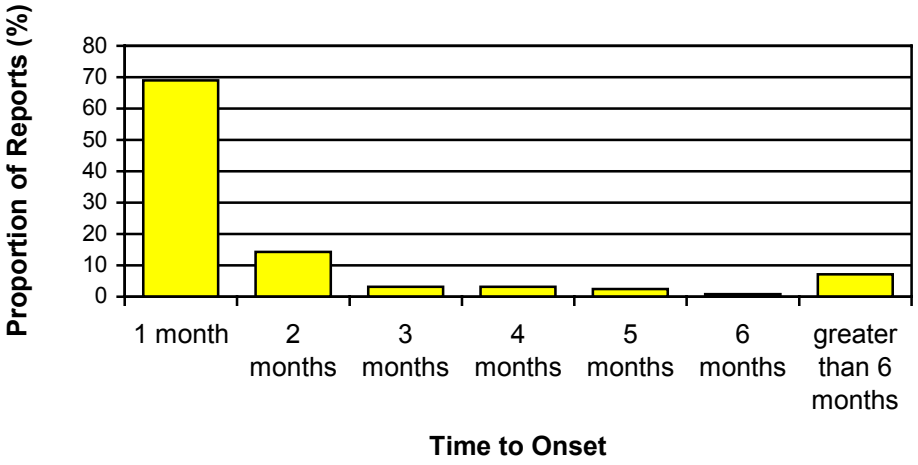


It is believed that product liability litigation and the resultant high level of media coverage of the issue of self-harm/suicidal behaviour, particularly in the US and UK, has contributed to the observed abrupt increase in the reporting rate of these events in 2002.

Time to onset and daily dose

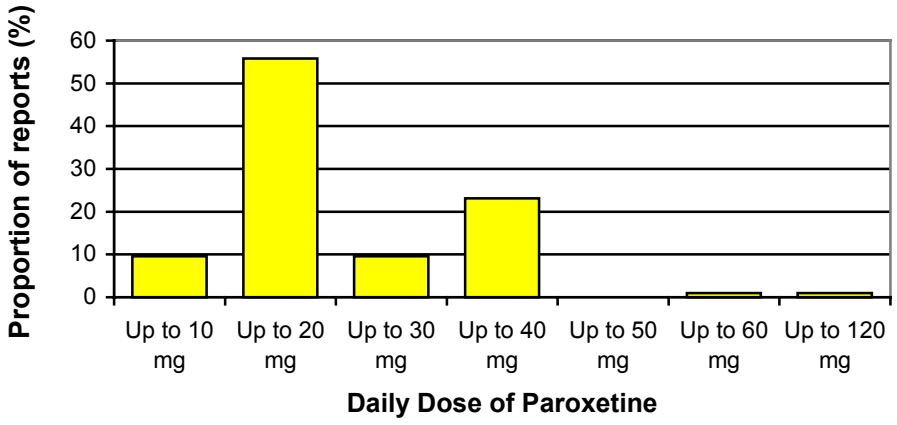
In order to review the time-to-onset and the daily dose of paroxetine at the time of the event in reports of self-harm/suicidal behaviour in adult patients, the 306 reports of completed suicide were manually reviewed and the results presented graphically (see Figure 3.10). Of the 306 reports reviewed, in 21 it was reported that the suicide had occurred after therapy with paroxetine had been discontinued and in 65 of the reports it was not specified whether the patient had received paroxetine prior to the suicide (these were primarily reports in which it was stated that a patient had taken paroxetine in overdose, but it had not been specified whether the patient had been taking the drug prior to the event). In an additional 89 of the reports, the patient had received paroxetine prior to the suicide but the time to onset was not provided, and in a further five reports the patient had committed suicide after taking paroxetine prescribed to someone else. In the remaining 126 cases which provided the information to enable the time-to-onset to be calculated, the suicide occurred within the first month of treatment in 69% (n = 87) of the reports (see Figure 3.10), and in 71% of those 87 cases the suicide occurred within 14 days of starting therapy.

Figure 3.10 Time-to-onset



The daily dose of paroxetine at the time of the suicide was provided in 104 of the 306 reports (34%). In an additional 21 cases the event occurred after therapy with paroxetine had been discontinued and in the remaining 181 cases the dosage was not specified. In the 104 reports where it was specified, the daily dosage ranged from 10 mg to 120 mg with 65% (68 cases) reporting the dose to be up to 20 mg. A graphical presentation of these data is provided in Figure 3.11.

Figure 3.11 Daily Dose



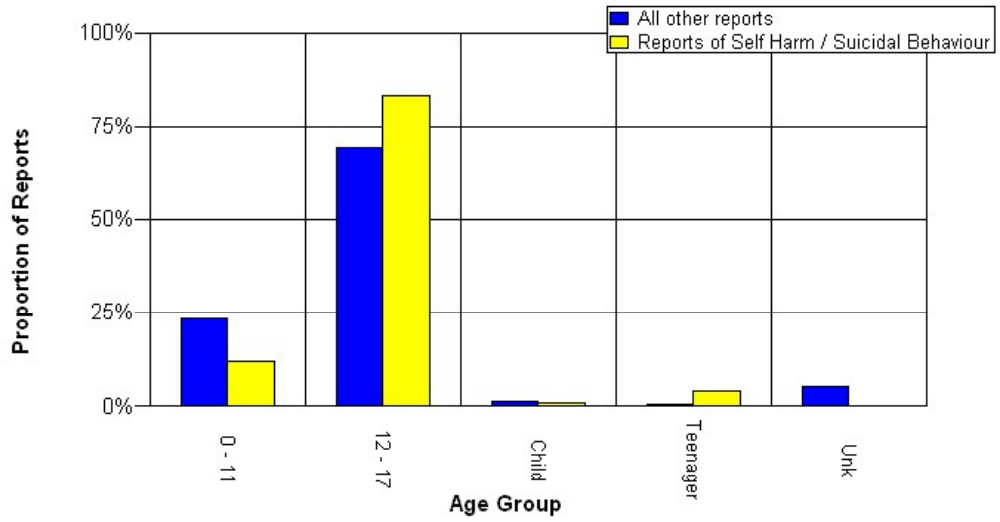
3.3.2.2. Self-harm/suicidal behaviour - paediatric patients

GSK received 126 reports of self-harm/suicidal behaviour in paediatric patients (up to and including 17 years of age) up to 31 May 2003 and this dataset is compared to 1,246 reports of other adverse events in the same age group received in the same period.

Age distribution

The age distribution of the reports in the paediatric dataset is presented in Figure 3.12. Note: the age groups "child" and "teenager" are categories used when a specific age was not provided but when it was known from the reporter's description that the category was appropriate. The reports in the unknown age group were identified as paediatric patients from remarks in the case narrative but a specific age or age group was not coded.

Figure 3.12 Age Distribution



A higher proportion of reports in the self-harm/suicidal behaviour paediatric dataset occurred in the 12-17 years age group (83.3%, n = 105) than in the "other events" paediatric dataset (69.5%, n = 866). Of the 105 reports of self-harm/suicidal behaviour in the 12-17 years age group, 52.4% (n = 55) were aged 12-15 years and 47.6% (n = 50) were aged 16-17 years.

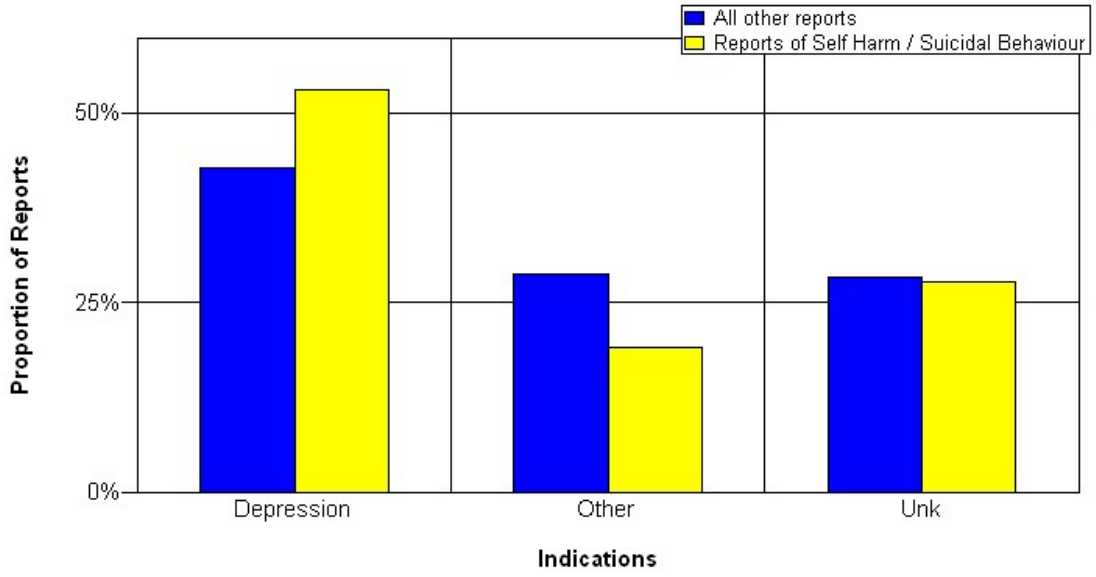
Gender

The gender split differs in the paediatric dataset from the adult dataset where a higher proportion of patients in the self-harm/suicidal behaviour dataset were male compared to the "other events" dataset. In the paediatric dataset however, a higher proportion of patients reporting self-harm/suicidal behaviour were female (59.5%, n = 75) compared to those reporting "other events" (54.1%, n = 674). This observation may possibly be explained by a link between the onset of self-harm/suicidal behaviour and increasing maturity and the generally more advanced maturity of females in a paediatric population.

Indication

The proportion of paediatric patients who were receiving paroxetine for depression (or depression plus other indications) was 53% (n = 67) in the self-harm/suicidal behaviour dataset, with 28% (n = 35) having an unknown indication and 19% (n = 24) another indication. In the "other events" dataset the proportion of patients receiving paroxetine for depression was 43% (n = 534), with 28 % (n = 354) having an unknown indication and 29% (n = 358) another indication, as presented in Figure 3.13.

Figure 3.13 Indication of depression



The proportion of patients who were receiving paroxetine for obsessive compulsive disorder (or OCD plus other indications) was lower in the self-harm/suicidal behaviour dataset than in the "other events" dataset, with 4.0% (n = 5) compared to 11.1% (n = 138) respectively.

Previous psychiatric history

The proportion of paediatric patients who had reportedly experienced self-harm/suicidal behaviour prior to the use of paroxetine showed a very similar pattern to the adult dataset presented previously, with the proportion higher in the self-harm/suicidal behaviour dataset (6.4%, n = 8) than the "other events" dataset (1.3%, n = 16).

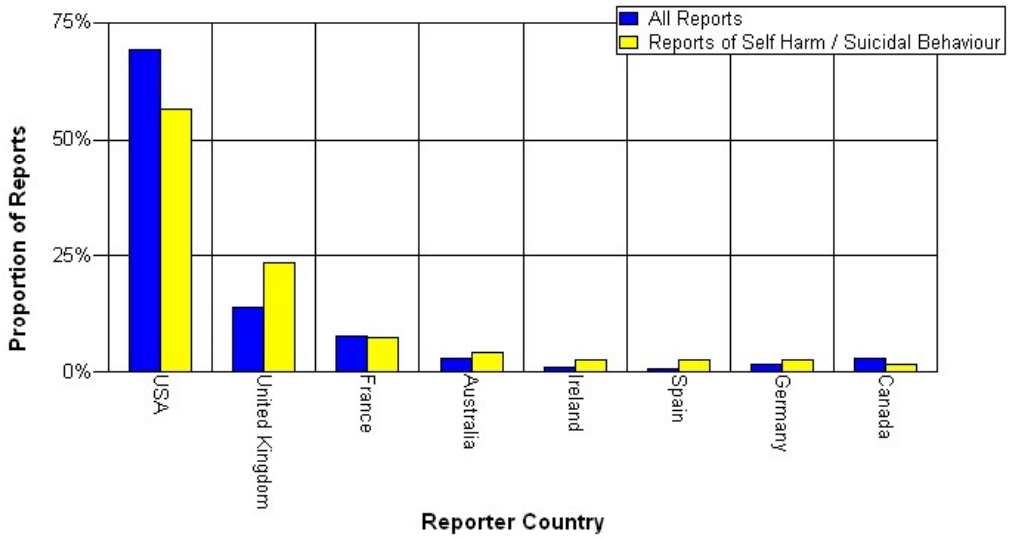
Concomitant psychotherapies

Differences in the pattern of psychotropic medication use was less marked in the paediatric population than the adult population, with 27.8% (n = 35) of patients in the self-harm/suicidal behaviour paediatric dataset having received concomitant psychotropic medication, compared to 25.0% (n = 311) of patients in the "other events" paediatric dataset.

Country of origin

As shown in Figure 3.14, the analysis of reporter country distribution for paediatric cases was similar to that for the adult population, in that relatively more self-harm/suicidal behaviour cases (23.0%, n = 29) were reported from the UK than for all cases overall from the UK (13.3%). However, since the numbers of cases was smaller, with only 126 paediatric self-harm/suicidal behaviour cases in total, the numbers of cases reported by the remaining countries was too small to know whether any observed differences were significant. The graph includes those countries which reported more than one case of self-harm/suicidal behaviour.

Figure 3.14 Distribution by country



Time to onset and daily dose

In order to review the time-to-onset and the daily dose of paroxetine at the time of the event in the paediatric reports of self-harm/suicidal behaviour, the 15 completed suicide cases were manually reviewed. Of the 15 cases reviewed, in two of the reports it was not specified whether the patient had received paroxetine prior to the suicide and in six reports the patient had received paroxetine prior to the suicide but the time to onset was not provided. In the remaining seven cases which provided the information to enable the time-to-onset to be calculated, the suicide occurred within the first month of treatment in three of the reports, within the second month in a single report, within the third month in two further cases and in the fourth month in the final report. The dosage at the time of the event was up to 20 mg in five of the six reports in which a dose was provided.

3.3.2.3. Summary of potential risk factors for self-harm/suicidal behaviour

In summary, the review of post-marketing reports of self-harm/suicidal behaviour in adult and paediatric patients receiving paroxetine revealed that adolescents and young adults were reported to be involved in relatively more self-harm/suicidal behaviour events compared to other events. In the paediatric dataset, relatively more females were reported to have experienced self-harm/suicidal behaviour as compared to other events. In contrast, in the adult dataset, although reports involving females still accounted for a majority of cases, relatively more males were reported to have experienced the events of interest when compared to the proportion of male patients experiencing other events. For both the adult/unspecified age dataset and the paediatric dataset the proportion of patients which were being treated for depression was greater in the self-harm/suicidal behaviour dataset than the "other events" dataset. The patients involved in self-harm/suicidal behaviour events were more likely to have a history of these events or to use concomitant psychotropic medications than patients in the "other events" dataset. Reporting of self-harm/suicidal behaviour increased abruptly in 2002 and a disproportionate number of these cases arose from the UK, probably reflecting the recent publicity given to these topics in that country. In adults, 69% of the events were reported to have occurred within the first month of paroxetine therapy and 71% of those occurred within the first two weeks of therapy (i.e. before any therapeutic improvement may be expected). The events were found not to be dose related and the majority of patients were receiving a low dose of up to 20 mg paroxetine/day.

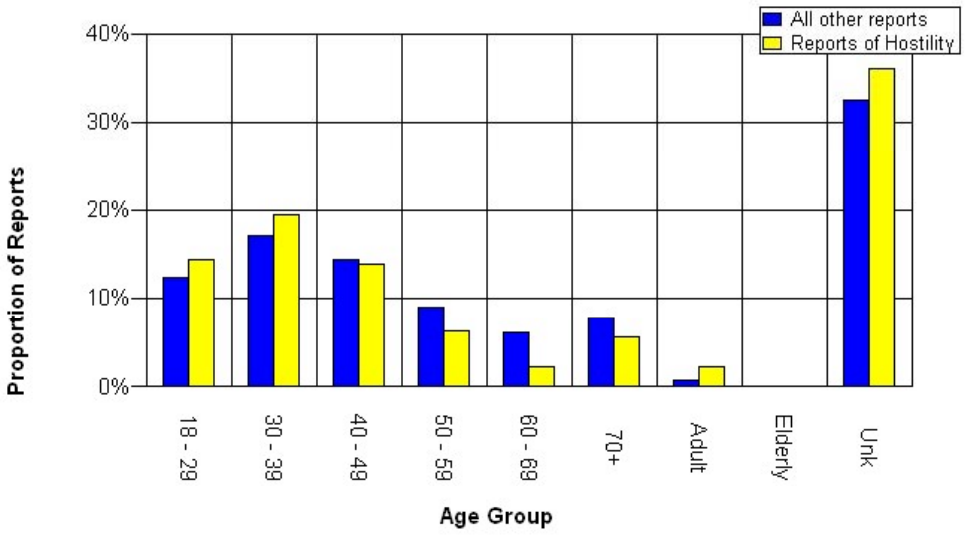
3.3.2.4. Hostility - adults plus patients of unspecified age

GSK received 685 reports of hostility in adults plus patients of unspecified age up to 31 May 2003 and this dataset is compared to 40,787 reports of other adverse events in adults or patients of unspecified age received in the same period.

Age distribution

The age distribution of the cases is presented in Figure 3.15. Note: the age groups "adult" and "elderly" are categories used when a specific age was not provided but when it was known that the category was appropriate.

Figure 3.15 Age Distribution



The graph shows that hostility was more commonly reported in younger adults, with the proportion of hostility cases reported in the 18-29 and 30-39 age groups being slightly higher than the proportion of "other events" in the same age groups.

Gender

The hostility dataset included a markedly greater proportion of male patients compared to the dataset of "other events", with 51.5% male (n = 353), 42.4% female (n = 290) and 6.1% unspecified gender (n = 42) compared to 26.0% male (n = 10,585), 63.0% female (n = 25,736) and 11.0% unspecified gender (n = 4,466).

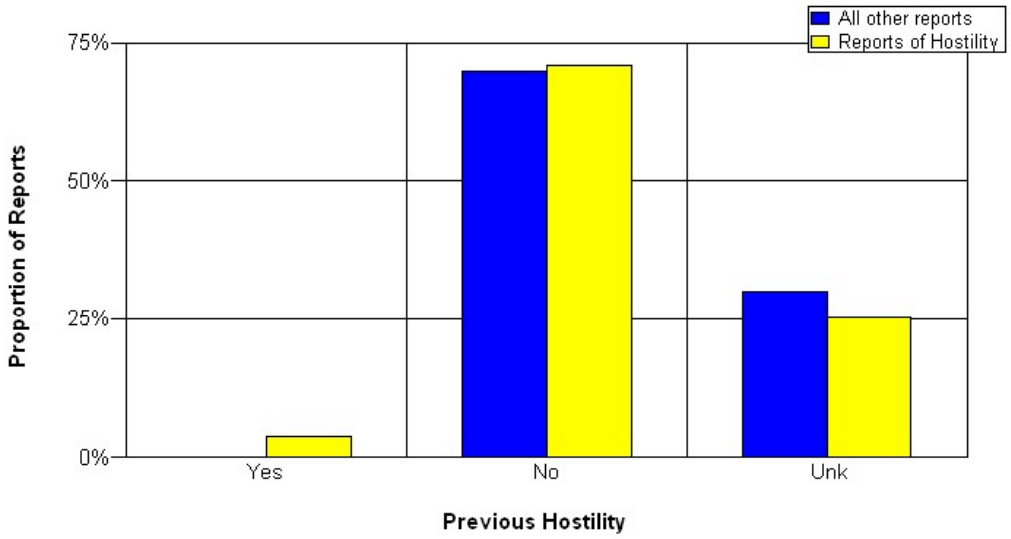
Indication

The proportion of patients who were receiving paroxetine for depression (or depression plus other indications) was similar in both datasets, 52.3% (n = 358) in the hostility dataset compared to 49.6% (20,240) in the "other events" dataset. The proportion of patients who were receiving paroxetine for obsessive compulsive disorder (or OCD plus other indications) was also similar in both datasets, 2.0% (14 cases) in the hostility dataset compared to 2.5% (1,023) in the "other events" dataset.

Previous psychiatric history

With regard to relevant medical history, in the hostility dataset 3.8% (n = 26) reported that the patient had experienced similar events previously (i.e. hostility was reported as medical history, a concurrent condition or as an indication for a concomitant medication) as compared to 0.1% (n = 35) in the "other events" dataset (Figure 3.16).

Figure 3.16 Relevant prior history



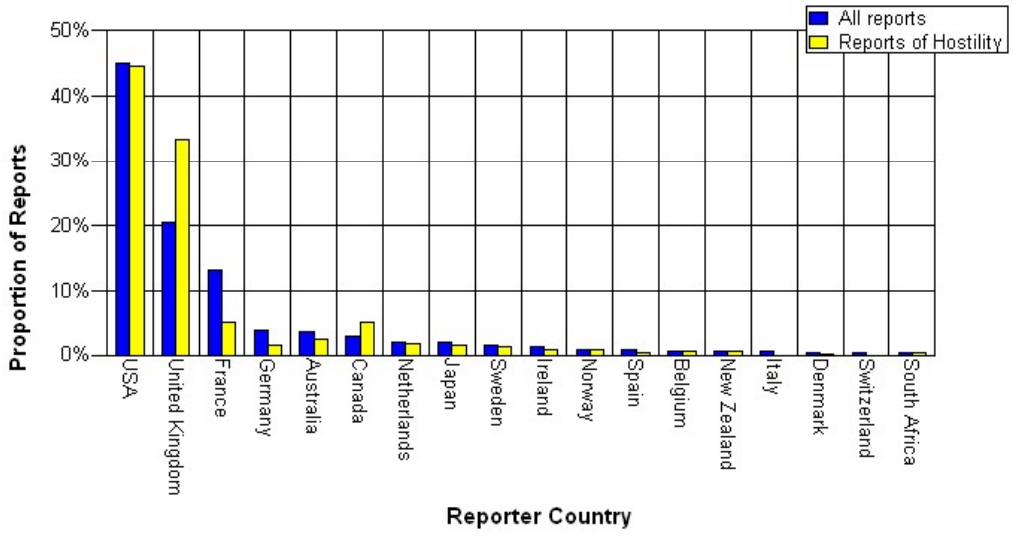
Concomitant pharmacotherapies

In the hostility dataset, the proportion of patients who had received concomitant psychotropic medication was 27.4% (n = 188) compared to 24.7% (n = 10,055) in the "other events" dataset.

Country of origin and proportion of cases received per year

The analysis of reporter country distribution presented in Figure 3.17 indicated that the proportion of hostility events received in the UK was greater than the proportion of all events received in the UK. The graph includes those countries which reported more than one case of hostility.

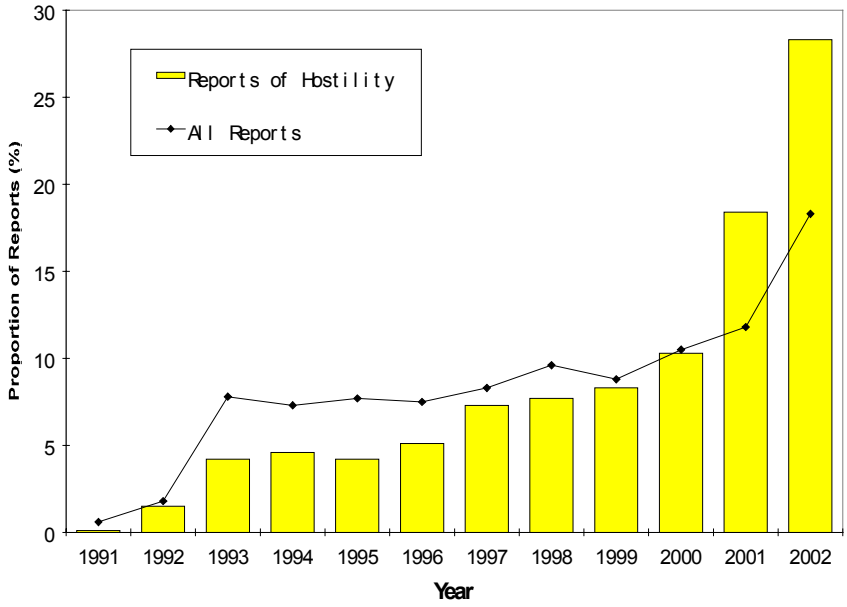
Figure 3.17 Distribution by Country



Although only 20% of all adult paroxetine reports arose from the UK, 33% of the adult hostility reports came from the UK.

To observe how the rate of reporting of hostility has changed over the marketed life of the drug, a graph of the proportion of these reports which have been received each year, since paroxetine was launched in 1991 until the end of 2002, is provided (see Figure 3.18). This graph presents the data for all hostility reports involving both adult and paediatric patients. The proportion of the total dataset of paroxetine reports, up to the end of 2002, which were received each year is provided so that the pattern of hostility reporting can be compared against the overall profile of reporting of all adverse events for paroxetine.

Figure 3.18 Proportion of reports received each year



It is believed that litigation and the resultant high level of media coverage of the issue of hostility, particularly in the US and UK, has contributed to the observed abrupt increase in the reporting rate of these events in 2001 and 2002.

Time to onset and daily dose

In order to review the time-to-onset and the dose at the time of the event in reports of hostility in adult patients, the 309 reports of physical violence (including reports of alleged murder) were manually reviewed and the results presented graphically (see Figure 3.19). Of the 309 reports reviewed:

70 documented that the event had occurred after therapy with paroxetine had been discontinued

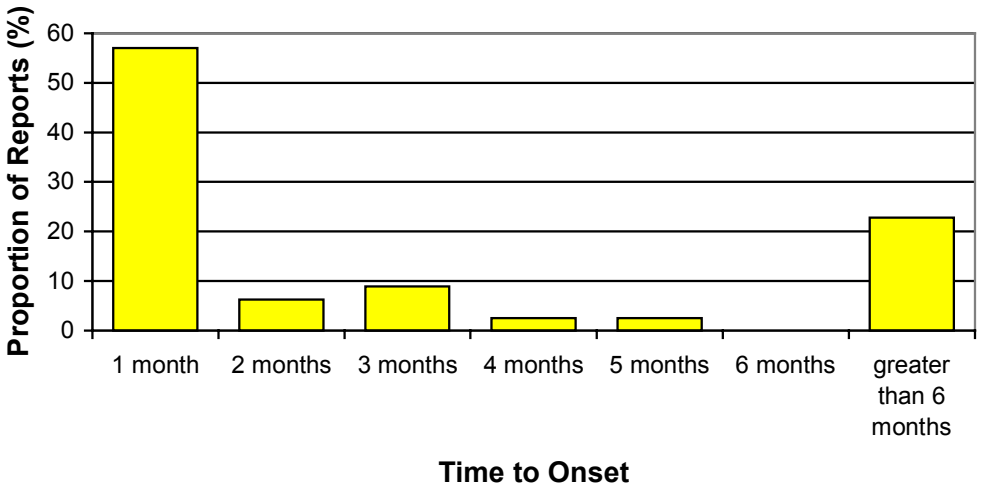
14 reports received via product liability litigation alleged that the patients were withdrawing or had discontinued therapy but it was not clear how many had discontinued or were in the process of withdrawing

In an additional five reports it was not specified whether the patient had received paroxetine prior to the event

In 141 reports the patient had received paroxetine prior to the event but the time to onset was not provided.

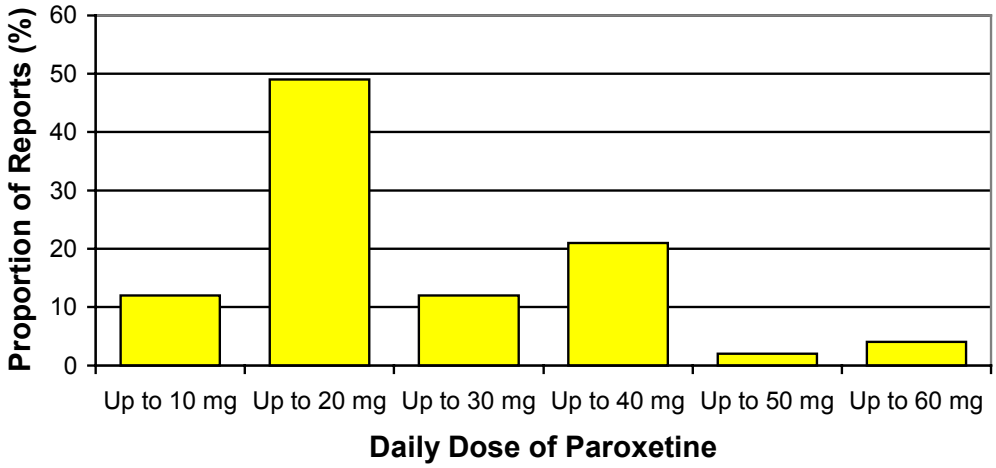
In the remaining 79 reports which provided the information to enable the time-to-onset to be calculated, the event occurred within the first month of treatment in 57.0% (n = 45), and in 29 of those 45 cases the event occurred within 14 days of starting therapy. In 22.8% (n = 18) the event developed after more than six months of therapy.

Figure 3.19 Time-to-onset



The daily dose of paroxetine at the time of the hostility event was provided in 109 of the 309 reports (35%), in an additional 70 reports the event occurred after therapy with paroxetine had been discontinued and in the remaining 130 reports the dosage was not specified. In the 109 reports where the daily dose was specified, it ranged from 10 mg to 60 mg (see Figure 3.20) with 61% (n = 66) of reports documenting a dose of up to 20 mg (a single report where the patient received 40 mg every other day was not included in the graph).

Figure 3.20 Daily dose



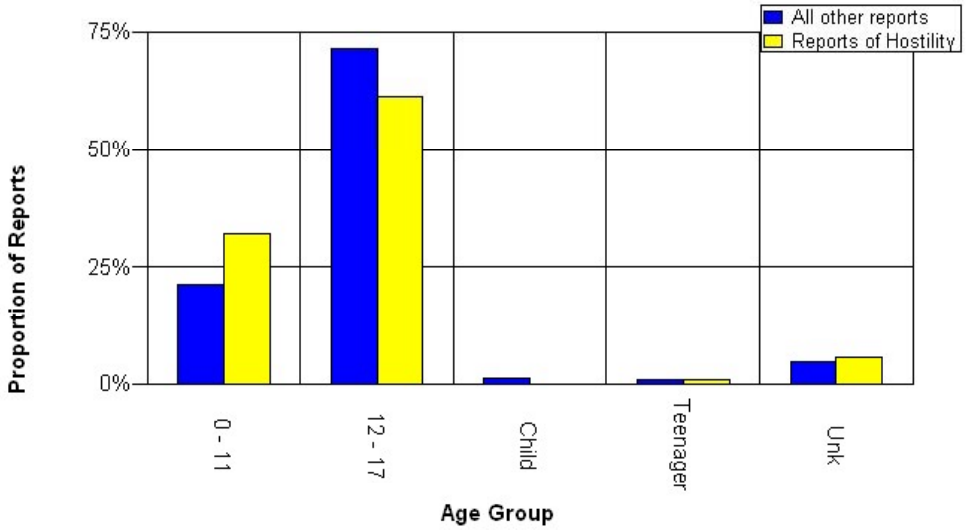
3.3.2.5. Hostility - paediatric patients

GSK received 106 reports of hostility in paediatric patients (up to and including 17 years of age) up to 31 May 2003 and this dataset is compared to 1,266 reports of other adverse events in the same age group received in the same period.

Age distribution

The age distribution of the reports in the paediatric dataset is presented in Figure 3.21. Note: the age groups "child" and "teenager" are categories used when a specific age was not provided but when it was known that the category was appropriate. The reports in the unknown age group were identified as paediatric patients from remarks in the case narrative but a specific age or age group was not coded.

Figure 3.21 Age Distribution

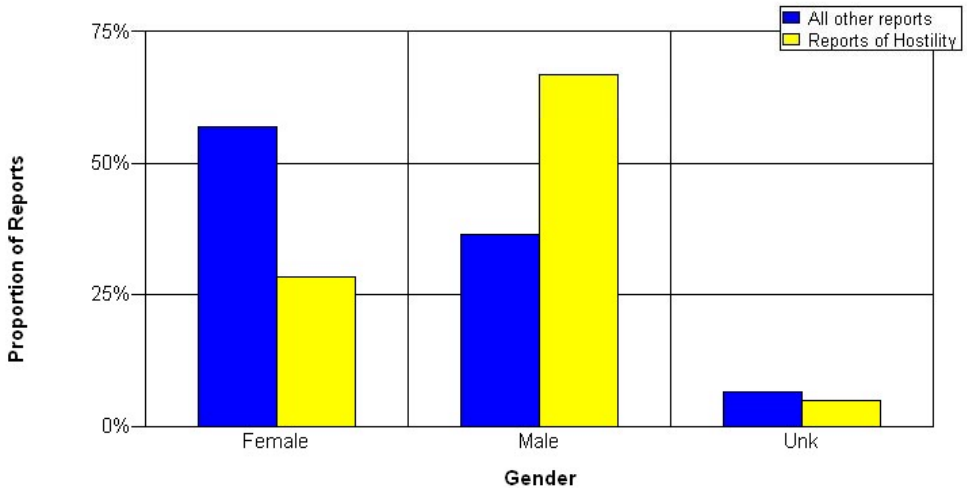


A higher proportion of reports in the hostility paediatric dataset comprised patients in the 0-11 years age group (32.1%, n = 34) than in the "other events" paediatric dataset (21.4%, n = 271). Of the 65 reports of hostility in the 12-17 years age group, 58.5% (n = 38) were aged 12-15 years and 41.5% (n = 27) were aged 16-17 years.

Gender

The disproportionately high number of male patients seen in the adult hostility dataset (51.5%) compared to the "other events" dataset (26.0%) was also seen in the paediatric hostility dataset. Figure 3.22 shows that 67.0% (n = 71) of paediatric reports of hostility referred to male patients as opposed to 36.6% (n = 463) of paediatric reports of "other events".

Figure 3.22 Gender distribution



Indication

The proportion of paediatric patients who were receiving paroxetine for depression (or depression plus other indications) was similar in both datasets, with 46.2% (n = 49) in the hostility dataset compared to 43.6% (n = 552) in the "other events" dataset. The proportion of patients who were receiving paroxetine for obsessive compulsive disorder (or OCD plus other indications) was also similar in the two datasets, with 13.2% (n = 14) in the hostility dataset and 10.2% (n = 129) in the "other events" dataset.

Previous psychiatric history

The proportion of paediatric patients who had reported hostility prior to the use of paroxetine was higher in the hostility dataset (13.2%, n = 14) than the "other events" dataset (1.3%, n = 16).

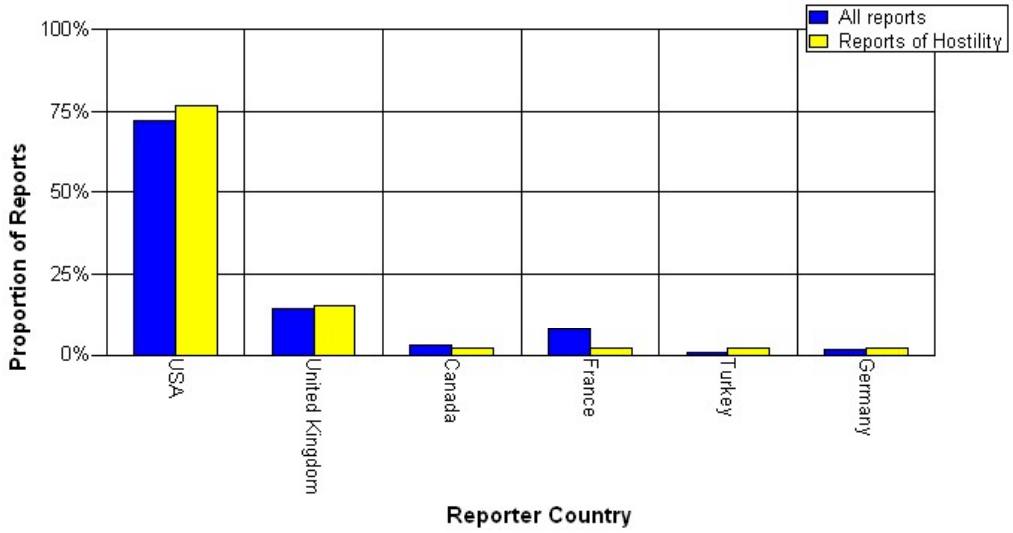
Concomitant pharmacotherapies

In the hostility dataset the proportion of patients who had received concomitant psychotropic medication was 40.6% (n = 43) compared to 23.9% (n = 303) in the "other events" dataset.

Country of origin

The analysis of reporter country distribution is presented in Figure 3.23. The proportion of paediatric hostility cases arising from the UK was only slightly elevated (15% of paediatric hostility reports and 13% of all paediatric event reports). The graph includes those countries which reported more than one report of hostility.

Figure 3.23 Distribution by country



Time to onset and daily dose

In order to review the time-to-onset and the daily dose of paroxetine at the time of the event in the paediatric reports of hostility, the case narratives of the 57 reports of physical violence (including alleged murder) were manually reviewed. In 15 of the 57 reports the patient had received paroxetine prior to the event but the time to onset was unknown, in a further two reports the patient had taken the paroxetine prescribed to someone else, and in an additional five reports the event had happened after paroxetine had been discontinued. In the 35 reports which provided significant information to enable the time-to-onset to be calculated, the hostility event occurred within the first month of treatment in 23 (65.7%) of the reports and within the second month in seven reports. There were single reports in which the events occurred in the third and fourth months and in three reports the events developed after greater than six months. The dosage at the time of the event was provided in 35 cases and 80% reported a daily dosage of up to 20 mg.

3.3.2.6. Summary of potential risk factors for hostility

In summary, the review of post-marketing reports of hostility in adult and paediatric patients receiving paroxetine revealed that children and young adults were reported to be involved in relatively more hostility events compared to other events. Both the paediatric and adult hostility datasets showed a significant shift to male patients when compared to the "other events" dataset. The proportion of patients which were being treated for depression was similar in both datasets, as was the proportion treated for obsessive compulsive disorder. The patients involved in hostility events were slightly more likely to

have a history of these events or to use concomitant psychotropic medications than patients in the "other events" dataset, with this difference being more pronounced in the paediatric dataset than the adult dataset. It seems likely that the abrupt increase in reporting of hostility observed during 2001 and 2002 can be partly attributed to increased publicity in the media and to litigation activity. As with the self-harm/suicidal behaviour dataset, a majority of the hostility events were reported to have occurred within the first month of paroxetine therapy and the events were found not to be dose related, with the majority of patients receiving a dose of up to 20 mg paroxetine/day.

3.4. Conclusions

3.4.1. Clinical trial data

In summary, analysis of the adult and paediatric clinical trial data relating to the risk of possibly suicide-related, self harm and hostility events demonstrated the following:

Adult clinical trial data

- Overall, the incidence of possibly suicide-related and self harm events was lower on paroxetine than other antidepressants, and was similar to that seen on placebo.
- Young adults have an increased risk of possibly suicide-related and self harm events, irrespective of treatment. Compared to placebo-treated patients, this effect appears to be heightened among patients treated with antidepressants. However, patients treated with paroxetine were at a lower risk compared to those treated with other SSRIs and other classes of antidepressants.
- Patients with baseline suicidal ideation were less likely to experience possibly suicide-related and self harm events if treated with paroxetine than if treated with placebo.
- Several other factors (e.g. suicidal history, prior psychotropic medication) were identified as being contributors to an increased risk of possibly suicide-related and self harm events, irrespective of whether patients were treated with paroxetine.
- In adults treated with paroxetine there was a low incidence of hostility, with the incidence of such events being similar to that seen with other antidepressants and with placebo. No particular subgroup of adults was identified as being at risk of hostility events with paroxetine treatment.
- There was no evidence of a relationship between the incidences of possibly suicide-related, self-harm and hostility events and the dose of paroxetine.

Paediatric clinical trial data

- The incidence of possibly suicide-related and self harm events was greater in paroxetine treated patients than in patients who received placebo, primarily in adolescents with major depressive disorder.

- Risk factors for possibly suicide-related and self harm events identified in the paediatric population included female gender, baseline suicidal ideation and baseline disease severity, but all were irrespective of treatment.
- There is insufficient active comparator data in the paediatric population to determine whether the effects are specific to paroxetine or are common to other antidepressants.
- In the paediatric population overall, paroxetine was associated with an increased risk of hostility compared to placebo. This was mainly seen in patients with OCD and in children under the age of 12 years.

3.4.2. Post-marketing data

- Reporting of hostility and self-harm/suicidal behaviour events increased abruptly in 2001 and 2002. However, in the context of the very large patient population treated with paroxetine, these events were still only very rarely reported in post-marketing use.

Adult post-marketing data

- A higher proportion of young adults were reported to have experienced self-harm/suicidal behaviour and hostility events compared to the proportion of young adults who were reported to have experienced other events.
- A higher proportion of male patients were reported to have experienced self-harm/suicidal behaviour and hostility events compared to the proportion of male patients who were reported to have experienced other events.
- A higher proportion of the following groups of patients reported self-harm/suicidal behaviour events compared to the proportion of the same groups of patients who reported other events: those who were being treated for depression, those with previous psychiatric history and those who concomitantly used other psychotropic medications.
- The majority of self-harm/suicidal behaviour and hostility events occurred within the first month of paroxetine therapy, and of these, the majority occurred within the first two weeks of therapy.
- Self-harm/suicidal behaviour and hostility events were found not to be dose related.

Paediatric post-marketing data

- A higher proportion of adolescents (12 – 17 years) were reported to have experienced self-harm/suicidal behaviour compared to the proportion of adolescents who were reported to have experienced other events.
- A higher proportion of children (up to 11 years) were reported to have experienced hostility compared to the proportion of children who were reported to have experienced other events.
- A higher proportion of female paediatric patients were reported to have experienced self-harm/suicidal behaviour compared to the proportion of female paediatric patients who were reported to have experienced other events.

- A higher proportion of male paediatric patients were reported to have experienced hostility compared to the proportion of male paediatric patients who were reported to have experienced other events.
- A higher proportion of the following groups of paediatric patients reported self-harm/suicidal behaviour compared to the proportion of the same groups of patients who reported other events: those who were being treated for depression and those with previous psychiatric history.
- A higher proportion of the following groups of paediatric patients reported hostility compared to the proportion of the same groups of patients who reported other events: those with previous psychiatric history and those who concomitantly used other psychotropic medications.