

## 12. QUESTION 12

*The fact that spontaneous reports were a mix of healthcare professional reports and non-medically validated reports is not acceptable. It was specified in the question that the MAHs should provide spontaneous reports separately from consumer reports. This applies to both the reports about suicides and to reports about withdrawal reactions.*

### Response

Question 2 and Question 6 of the Article 31 Referral (26 June 2003) requested an analysis of all data relating to the risk of self-harm, hostility, suicidal behaviour, and withdrawal reactions with paroxetine using data from all available sources including clinical trials, spontaneous reporting, observational studies, volunteer studies and consumer reports. There was no specified requirement within the questions to treat spontaneous reports from healthcare professionals and consumer reports separately within the analysis. On 25 July 2003, GSK submitted an analysis plan to the Rapporteur and Co-rapporteur detailing the proposed format and content of the Consolidated Response Document. In the analysis plan, GSK stated that all spontaneous reports received by GSK for paroxetine, including those from unsolicited notifications (ie. health professionals, consumers, lawyers), published literature and regulatory authorities, would be included within the scope of the review and that they would be considered together under the heading of spontaneous reports. This approach was considered the most appropriate by GSK on the basis that a large proportion of the reports came from consumers and it was considered that splitting the data by reporter could potentially reduce the power of the analysis to identify any risk factors. The nature of the symptoms under investigation were also considered by GSK to be subjective (particularly in relation to withdrawal reactions) and therefore consumer reports were considered to be of equal value to the analysis without medical interpretation by the patient's physician. No specific comment was received from the Rapporteur or Co-rapporteur on this proposal that spontaneous reports from all sources be considered together, following the submission of the analysis plan (25 July 2003) or during the subsequent meeting with the Rapporteur and Co-rapporteur (30 July 2003).

GSK have, however, at the request of the CPMP provided separate analyses of the risk factors of self-harm/ suicide-related events and withdrawal reactions in adult and paediatric populations for the medically validated reports and consumer reports. This analysis is provided in sections [12.1](#) to [12.3](#) below.

### 12.1. Strategy of Analysis

The overall datasets and methodology used in the analysis of risk factors in the post-marketing reports are the same as those described in sections 2.5, 3.3 and 6.5 of the Consolidated Response Document submitted by GSK on 01 September 2003. For the purpose of this analysis, the original datasets of post-marketing reports have been split into those reports received from healthcare professionals (HCPs) ie. physicians, pharmacists, dentists, the medical literature and regulatory authorities, and those received from consumers or other non-medically validated sources (hereafter referred to as

"reports received from consumers"). It should be noted, however, that the GSK Clinical Safety Database is a dynamic database and that follow-up for individual case reports may have been received since the datalock point of the initial analysis. As a result of receipt of this follow-up information, a small number of reports may have moved groups within a specific analysis, or may have become medically validated since the datalock point of the initial analysis submitted on 01 September 2003. Hence, the absolute numbers presented in this new response may differ slightly to those previously submitted.

## **12.2. Results of Analysis of Potential Risk Factors of Self-harm and Possible Suicide Related Events.**

### **12.2.1. Self-harm/suicidal behaviour - adults and patients of unspecified age**

GSK received 1,413 reports of self-harm/suicidal behaviour in adults plus patients of unspecified age up to 31 May 2003. Of these reports, 997 (71.0%) were received from HCPs and 416 (29.0%) were from consumers. During the same period, GSK received 40,056 reports of "other events" in adults plus patients of unspecified age received in the same period, of which 26,968 (67.0%) were received from HCPs and 13,088 (33.0%) were received from consumers. In this analysis of risk factors, the dataset of 997 reports from HCPs documenting self-harm/suicidal behaviour is compared with the 26,968 HCP-confirmed reports of "other events". Similarly, the 416 consumer reports of self-harm/suicidal behaviour are compared with the 13,088 consumer reports of "other events".

#### **12.2.1.1. Age distribution**

The age distribution of the adult dataset is presented in [Figure 12.1](#) (HCP confirmed reports) and [Figure 12.2](#) (consumer reports). Note: the age groups "adult" and "elderly" are used when a specific age was not provided but when it was known from the reporter's description that the category was appropriate.

Figure 12.1 Age distribution – reports received from healthcare professionals

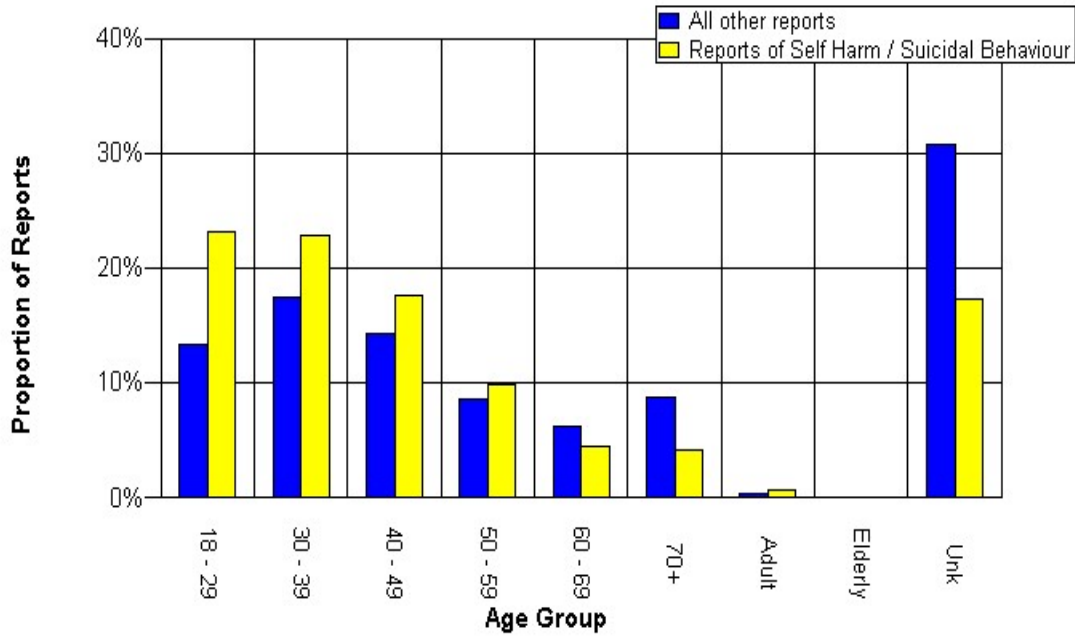


Figure 12.2 Age distribution – reports received from consumers

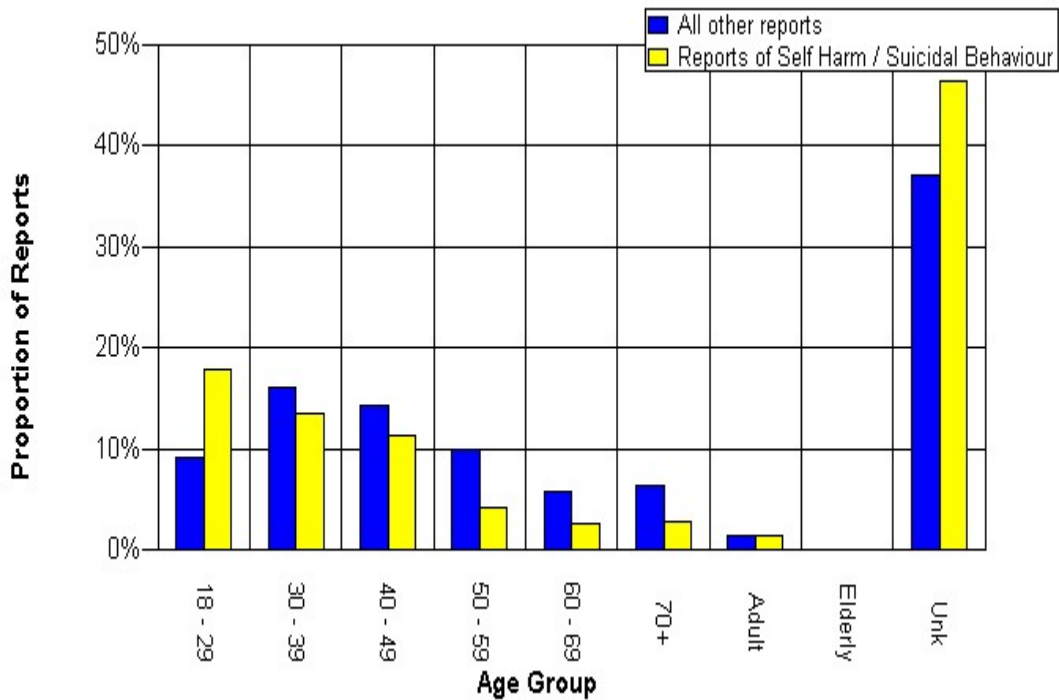


Figure 12.1 and Figure 12.2 both show that self-harm/suicidal behaviour events were more frequently reported in young adults with 23.2% (n = 231) of HCP reports and 17.8% (n = 74) of consumer reports being reported in the 18-29 years age group. This compares to 13.4% (n = 3,602) of HCP reports and 9.2% (n = 1,207) of consumer reports reporting "other events" in the same age group. It should be noted, however, that the difference between the number of self-harm/suicidal behaviour events observed in the 18-29 and the 30-39 age groups in those reports received from HCPs was only very small.

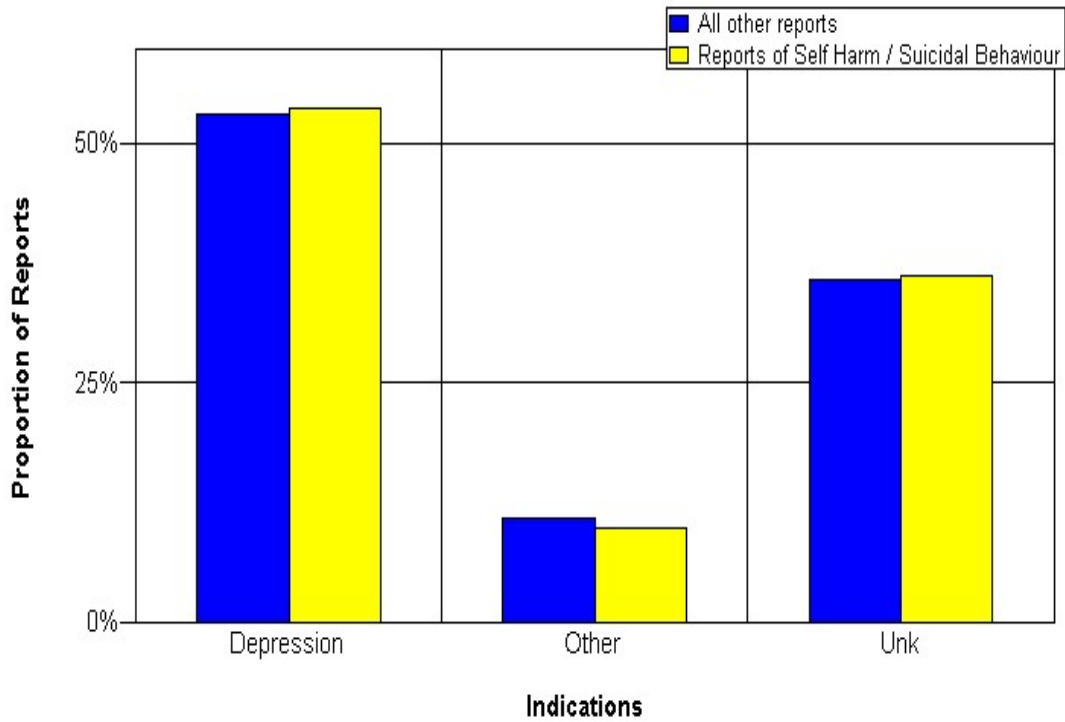
#### **12.2.1.2. Gender**

The self-harm/suicidal behaviour dataset included a greater proportion of male patients compared to the dataset of "other events", when examining both the HCP reports and the consumer reports. Of the 997 HCP reports of self-harm/suicidal behaviour, 35.5% (n = 353) were male, 54.5% (n = 543) were female and 10.0% (n = 101) were of unspecified gender, compared to 24.4% (n = 6,584) male, 61.4% (n = 16,549) female and 14.2% (n = 3,835) unspecified gender in the "other events" dataset. Similarly, of the 416 consumer reports of self-harm/suicidal behaviour, 39.2% (n = 163) were male, 55.1% (n = 229) female and 5.8% (n = 24) unspecified gender, compared to 29.3% (n = 3,837) male, 66.5% (n = 8,708) female and 4.2% (n = 543) unspecified gender in the "other events" dataset.

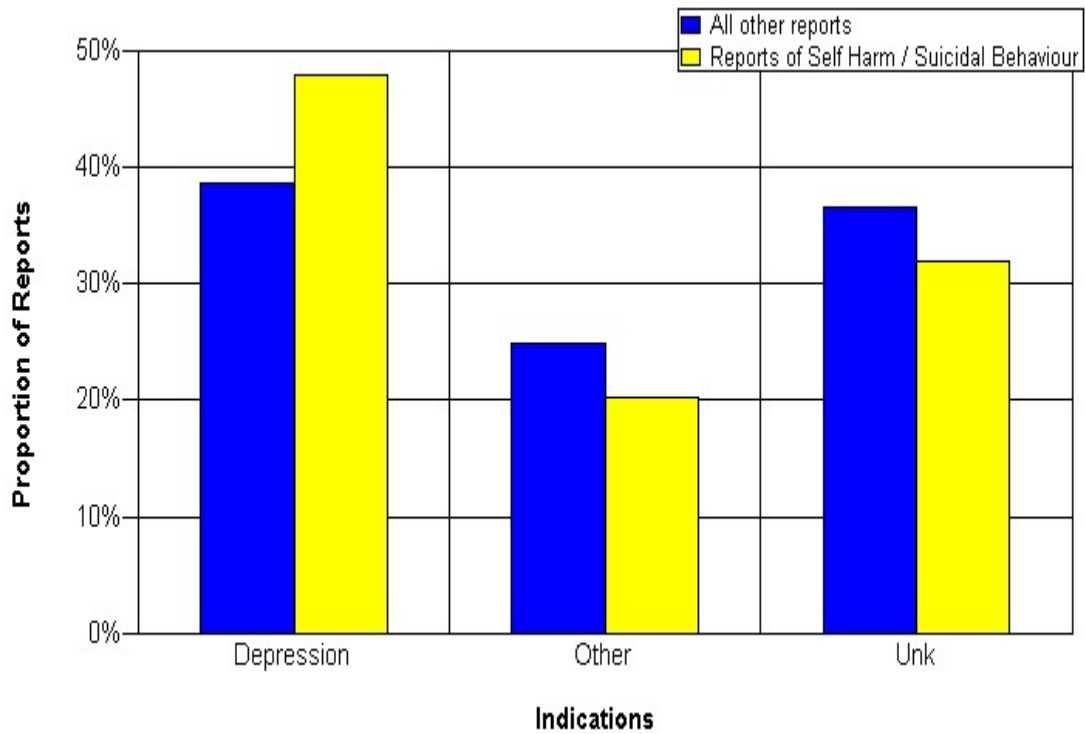
#### **12.2.1.3. Indication**

The proportion of patients who were receiving paroxetine for depression (or depression plus other indications) in the self-harm/suicidal behaviour dataset was similar for those reports received from an HCP (Figure 12.3) and those received from a consumer (Figure 12.4). In 54.0% (n = 536) of reports received from a HCP the patient was receiving paroxetine for depression (or depression plus other indications), with 36.0% (n = 9,674) having an unknown indication and 10.0% (n = 99) another indication. This compares to 53.0% (n = 14,344) of patients in the "other events" dataset with an indication of depression, 36.0% (n = 9,674) having an unknown indication and 11.0% (n = 2,950) with another indication. Similarly, in 48.0% (n = 199) of reports received from consumers the patient was receiving paroxetine for the treatment of depression, with 32.0% (n = 133) having an unknown indication and 20.0% (n = 84) another indication, compared to 39.0% (n = 5,052) of patients in the "other events" dataset having an indication of depression, 37.0% (n = 4,782) having an unknown indication and 25.0% (n = 3,254) another indication. A slightly higher proportion of patients with self-harm/suicide related events were reported to have received paroxetine for depression when compared with the "other events." This trend was more apparent for the consumer reports.

**Figure 12.3 Indication of depression – reports received from healthcare professionals**



**Figure 12.4 Indication of depression – reports received from consumers**

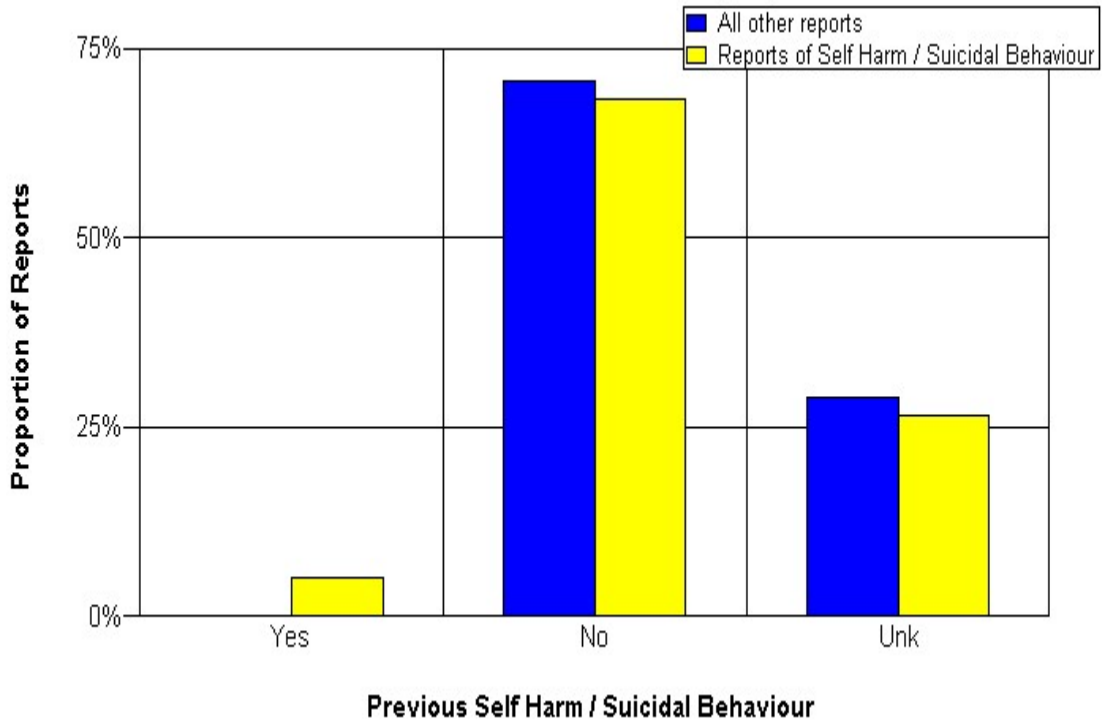


The proportion of patients receiving paroxetine for OCD (or OCD plus other indications) in the self-harm/ suicidal behaviour dataset was also found to be similar for those reports received from HCPs and those received from consumers. In 1.4% (n = 14) of reports received from a HCP the patient was receiving paroxetine for OCD (or OCD plus other indications), with 36.3% (n = 362) having an unknown indication and 62.3% (n = 621) another indication. In 2.4% (n = 10) of reports received from consumers the patient was receiving paroxetine for the treatment of OCD, with 32.0% (n = 133) having an unknown indication and 65.6% (n = 273) another indication. This was comparable to the "other events" dataset with 2.1% (n = 563) of HCP reports documenting an indication of OCD and 3.5% (n = 452) of consumer reports.

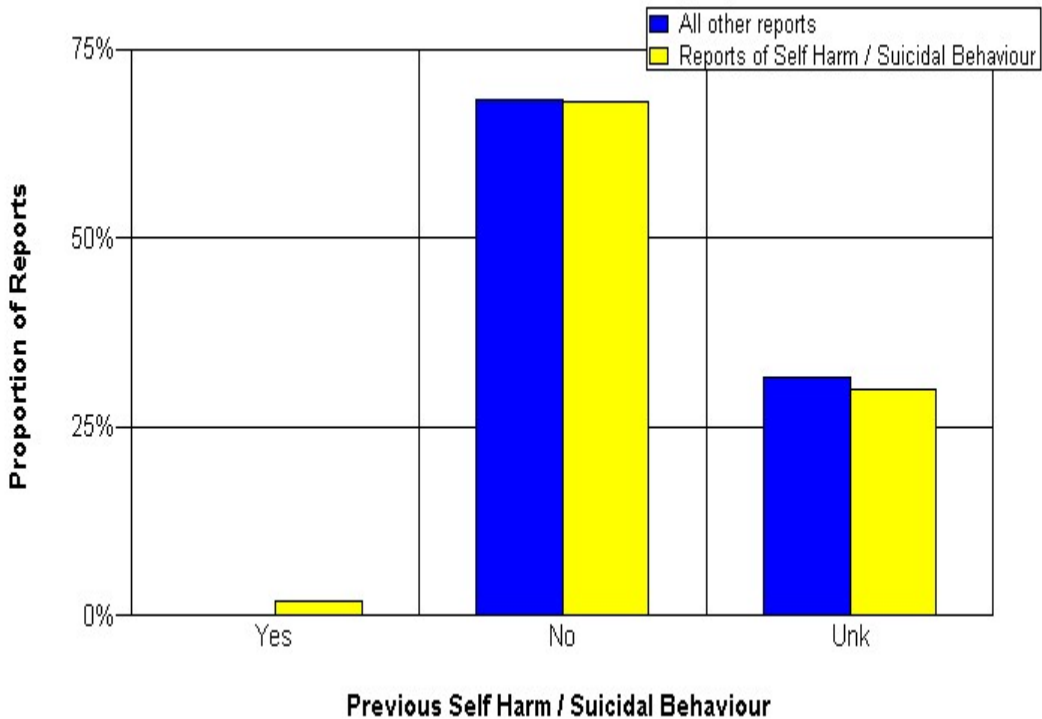
#### **12.2.1.4. Previous psychiatric history**

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 for both the HCP and consumer reports, as shown in [Figure 12.5](#) (HCP reports) and [Figure 12.6](#) (consumer reports).

**Figure 12.5 Relevant prior history – reports received from healthcare professionals**



**Figure 12.6 Relevant prior history – reports received from consumers**



Of the HCP-confirmed reports of self-harm/suicidal behaviour, 5.1% (n = 51) documented that the patient had experienced similar events previously (ie. self-harm/suicidal behaviour was reported as medical history, a concurrent condition or as an indication for a concomitant medication) as opposed to 0.2% (n = 57) in the HCP "other events" dataset. Similarly, 1.9% (n = 8) of reports of self-harm/suicidal behaviour received from consumers documented that the patient had experienced similar events previously, compared to 0.1% (n = 15) reports in the "other events" dataset.

#### **12.2.1.5. Concomitant pharmacotherapies**

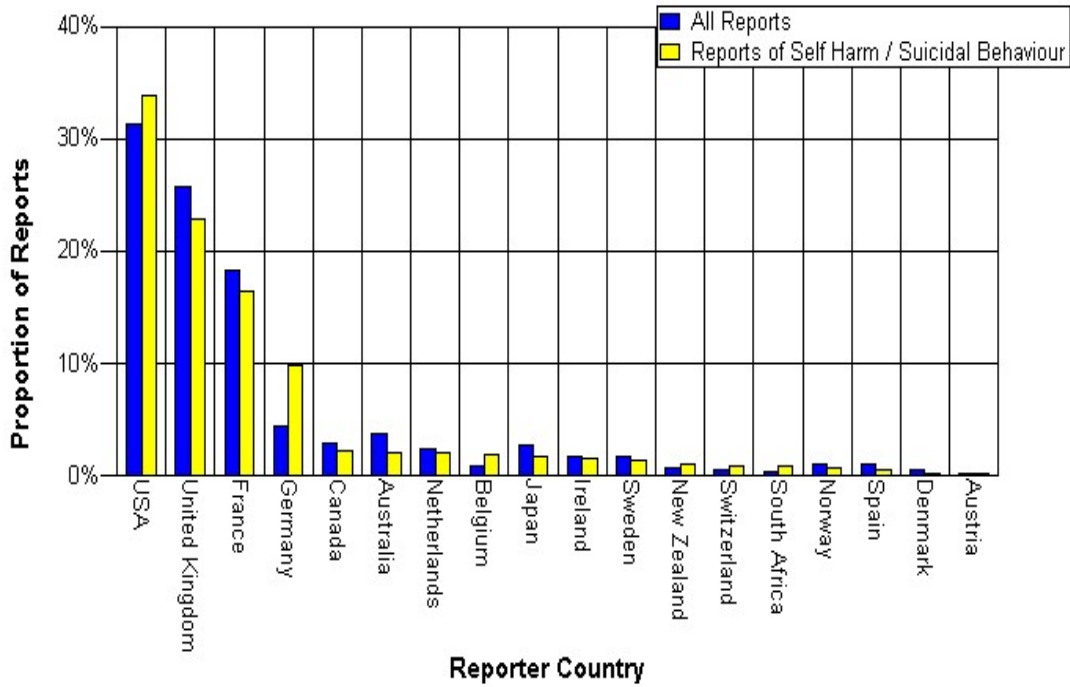
A notable difference was observed when comparing the proportion of patients who were receiving other psychotropic medications in the self-harm/suicidal behaviour dataset compared to the "other events" dataset when examining reports received from HCPs. Of those reports in the self-harm/suicidal behaviour dataset, 48.8% (n = 487) documented one or more psychotropic medications, compared to 27.1% (n = 7,295) of reports in the "other events" dataset. The difference was not so large when looking at consumer reports with 20.2% (n = 84) of reports of self-harm/suicidal behaviour documenting one or more psychotropic medications compared to 18.3% (n = 2,397) of reports in the "other events" dataset.

#### **12.2.1.6. Country of origin and proportion of reports received each 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 12.7](#) and [Figure 12.8](#), respectively, show the distribution of HCP and consumer reports by country. The graphs include those countries which reported more than one case of self-harm/suicidal behaviour.



**Figure 12.7 Distribution by country – reports received from healthcare professionals**



**Figure 12.8 Distribution by country – reports received from consumers**

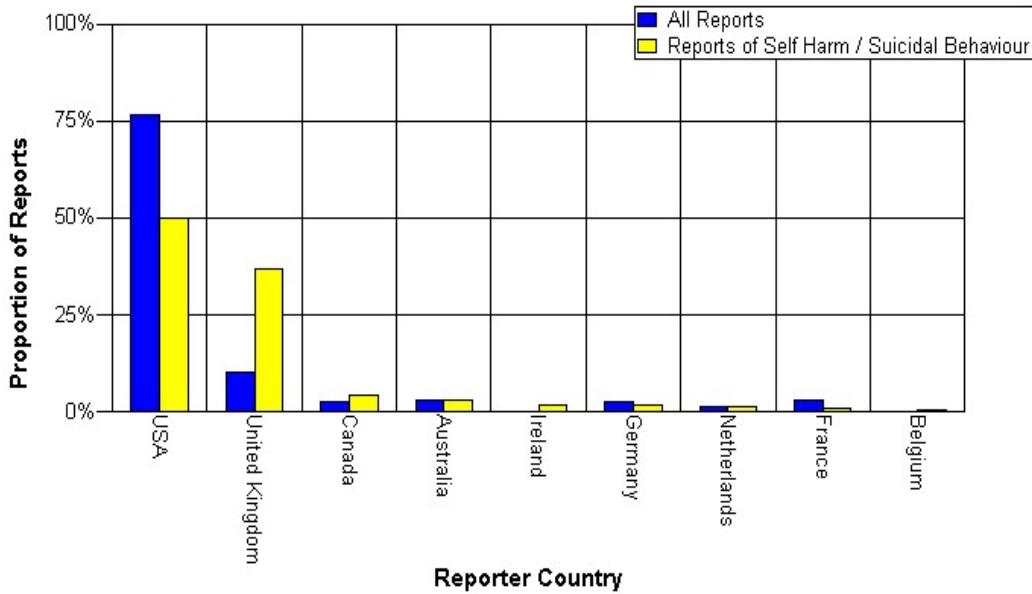


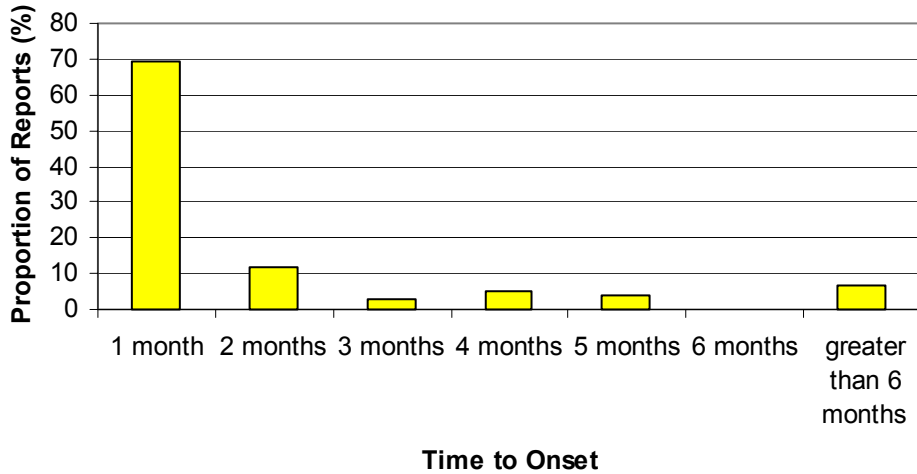
Figure 12.7 shows that the proportion of self-harm/suicidal behaviour events received from HCPs in Germany was greater than the proportion of all events received from that country, with 9.8% of reports of self-harm/suicidal behaviour coming from Germany and only 4.3% of all reports. A similar, but less marked trend was seen for the HCP reports from the USA, where 30.9% of all HCP adverse event reports came from the USA and 33.7% of those reports involving self-harm/suicidal behaviour events. With regard to the consumer reports (Figure 12.8), in the USA relatively fewer reports of self-harm/suicidal behaviour came from consumers when compared with the proportion of all reports of adverse events that came from that country. In contrast, in the UK consumers had reported relatively more events of self-harm/suicidal behaviour. This observation within the UK is most likely the result of increased reporting of self-harm/suicidal behaviour events by consumers following media attention, in particular BBC Panorama programmes broadcast on television in the UK in 2002 and 2003.

It is believed that the difference in overall reporting rate per country are most likely to be the result of the publicity given to these types of events in particular populations within these countries, rather than being an indicator of specific race vulnerability.

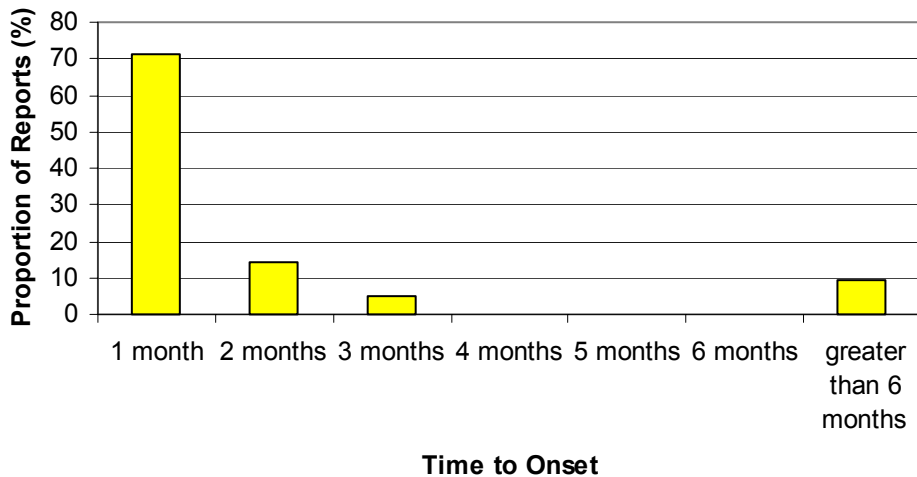
#### **12.2.1.7. Time-to-onset and daily dose**

In order to review the time-to-onset and 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 in this population, were manually reviewed for relevant information. Of these 306 reports, 82.0% (n = 252) were received from a HCP and 18.0% (n = 54) were consumer reports. In 24 reports (22 HCP reports, 2 consumer reports) it was reported that the suicide had occurred after therapy with paroxetine had been discontinued, and in 76 reports (68 HCP reports, 8 consumer reports) it was not specified whether the patient had received paroxetine prior to the suicide. In an additional 78 reports (55 HCP reports, 23 consumer reports) the patient had received paroxetine prior to the suicide but the time-to-onset was not provided, and in a further five reports (all received from a HCP) the patient had committed suicide after taking paroxetine prescribed to somebody else. The remaining 123 reports, which comprised of 102 HCP reports and 21 consumer reports, provided enough information to calculate the time-to-onset. No significant differences were seen between reports received from HCPs (Figure 12.9) or those received from consumers (Figure 12.10). In 69.6% (n = 71) of the 102 HCP reports, the suicide occurred within the first month of treatment, with 53.9% (n = 55) occurring within 14 days. Similarly, in 71.4% (n = 15) of the 21 consumer reports the suicide occurred within the first month of treatment, with 38.1% (n = 8) occurring within 14 days of starting therapy.

**Figure 12.9 Time-to-onset – reports received from healthcare professionals**

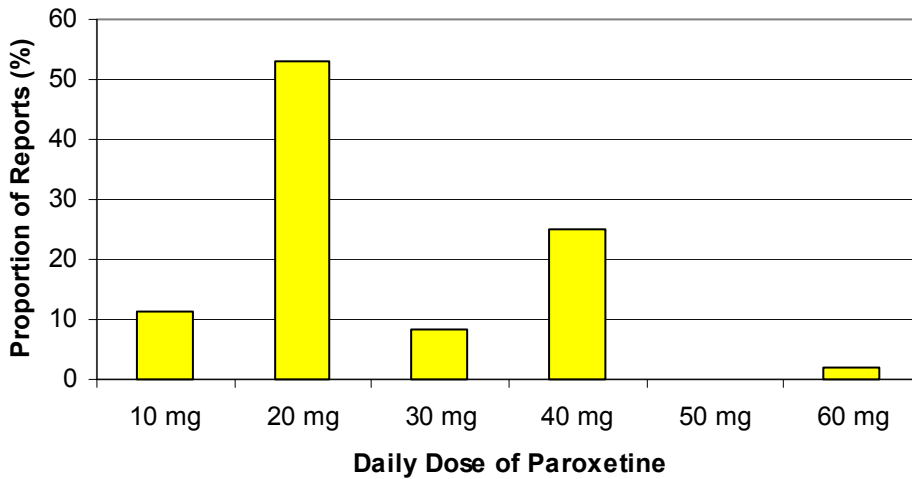


**Figure 12.10 Time-to-onset – reports received from consumers**

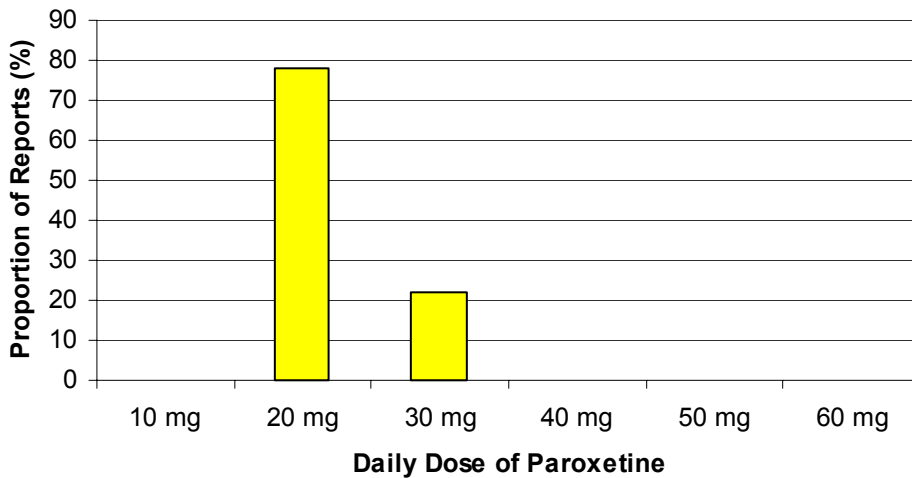


The daily dose of paroxetine at the time of the suicide was provided in 105 of the 306 reports (96 HCP reports, 9 consumer reports). In an additional 24 reports (22 HCP reports, 2 consumer reports) the event occurred after paroxetine had been discontinued and in the remaining 177 reports (134 HCP reports, 43 consumer reports) the dosage was not specified. In the 105 reports where it was specified, the daily dose ranged from 10 mg to 60 mg, with 69 cases (62 HCP reports, 7 consumer reports) reporting the dose to be up to 20 mg. A graphical presentation of the data for HCP reports is provided in [Figure 12.11](#) and for consumer reports in [Figure 12.12](#).

**Figure 12.11 Daily dose – reports received from healthcare professionals**



**Figure 12.12 Daily dose – reports received from consumers**



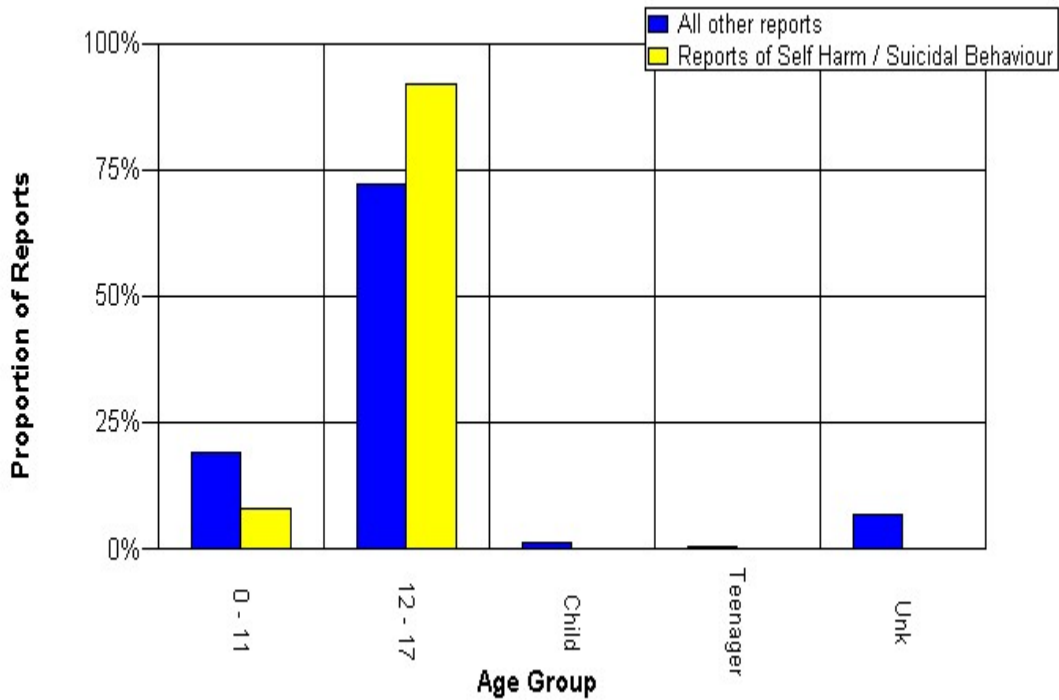
**12.2.2. Self-harm/suicidal behaviour - paediatric patients**

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. Of these reports 59.5% (n = 75) were received from HCPs and 40.5% (n = 51) from consumers or other non-medically validated sources. A total of 1,248 reports of "other events" in the same age group were received in the same time period, of which 71.8% (n = 896) were received from HCPs and 28.2% (n = 352) were received from consumers. In this analysis of risk factors, the 75 reports of self-harm/suicidal behaviour received from HCPs is compared with the 896 reports of "other events" received from HCPs. Likewise, the 51 reports of self-harm/suicidal behaviour received from consumers are compared with the 352 reports of "other events" received from consumers.

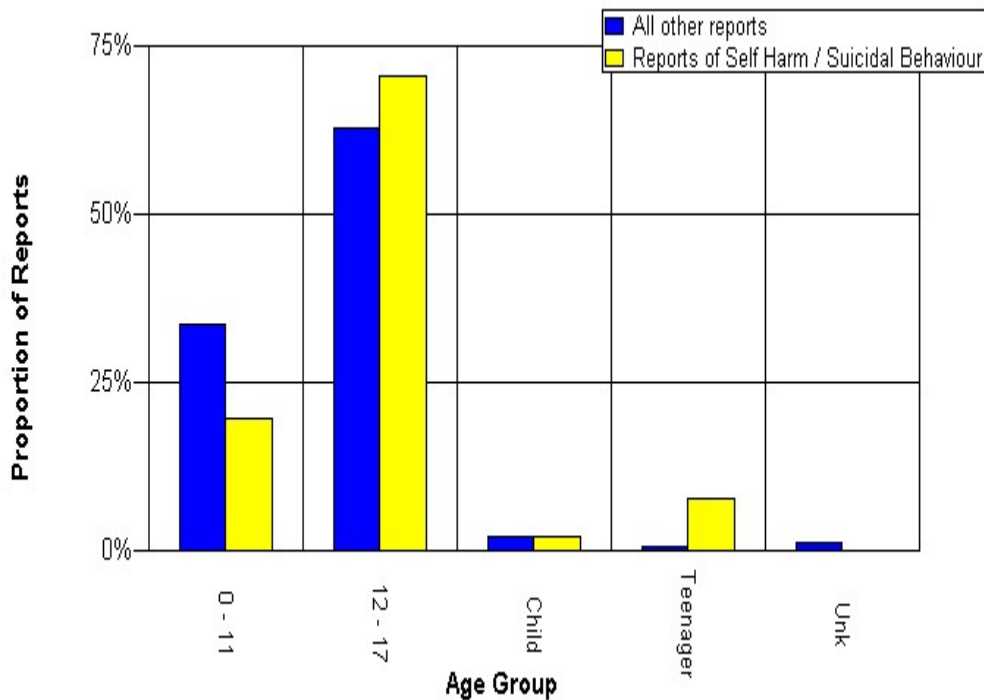
12.2.2.1. Age distribution

The age distribution of the reports received in the paediatric dataset is presented in [Figure 12.13](#) (HCP reports) and [Figure 12.14](#) (consumer reports). Note: the age groups "child" and "teenager" are categories used when a specific age was not provided but when it was known from the reporters 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 12.13 Age distribution – reports received from healthcare professionals



**Figure 12.14 Age distribution – reports received from consumers**



A higher proportion of reports in the self-harm/suicidal behaviour paediatric dataset involved patients in the 12-17 years age group when compared with the "other events" paediatric dataset. Ninety-two percent (n = 69) of HCP reports and 70.6% (n = 36) of consumer reports documenting self-harm/suicidal behaviour occurred in patients aged 12-17 compared to 72.2% (n = 647) of HCP reports and 62.8% (n = 221) of consumer reports in the "other events" dataset.

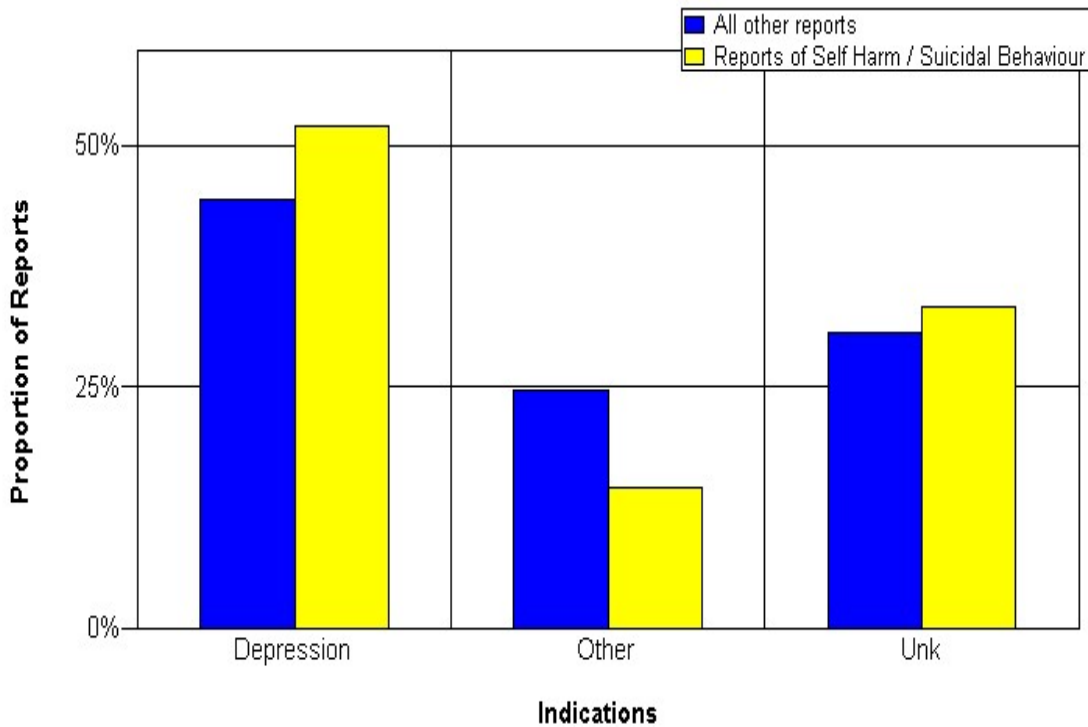
**12.2.2.2. Gender**

In the adult dataset a higher proportion of patients in the self-harm/suicidal behaviour dataset were male compared to the "other events" dataset for both the HCP and consumer reports. However, in the paediatric dataset a higher proportion of patients reporting self-harm/suicidal behaviour were female. This was observed for both HCP and consumer reports, with 62.7% (n = 47) of HCP reports of self-harm/suicidal behaviour in the paediatric dataset occurring in female patients, 36.0% (n = 27) occurring in males and 1.3% (n = 1) occurring in patients of unspecified gender, compared to 55.6% (n = 498) female, 36.3% (n = 325) male and 8.2% (n = 73) unspecified gender in the "other events" dataset. Similarly, 56.9% (n = 29) of consumer reports of self-harm/suicidal behaviour in the paediatric dataset occurred in females, 35.3% (n = 18) in males and 7.9% (n = 4) in patients of unspecified gender, compared to 50.0% (n = 176) female, 47.4% (n = 167) male and 2.6% (n = 9) unspecified gender in the "other events" dataset.

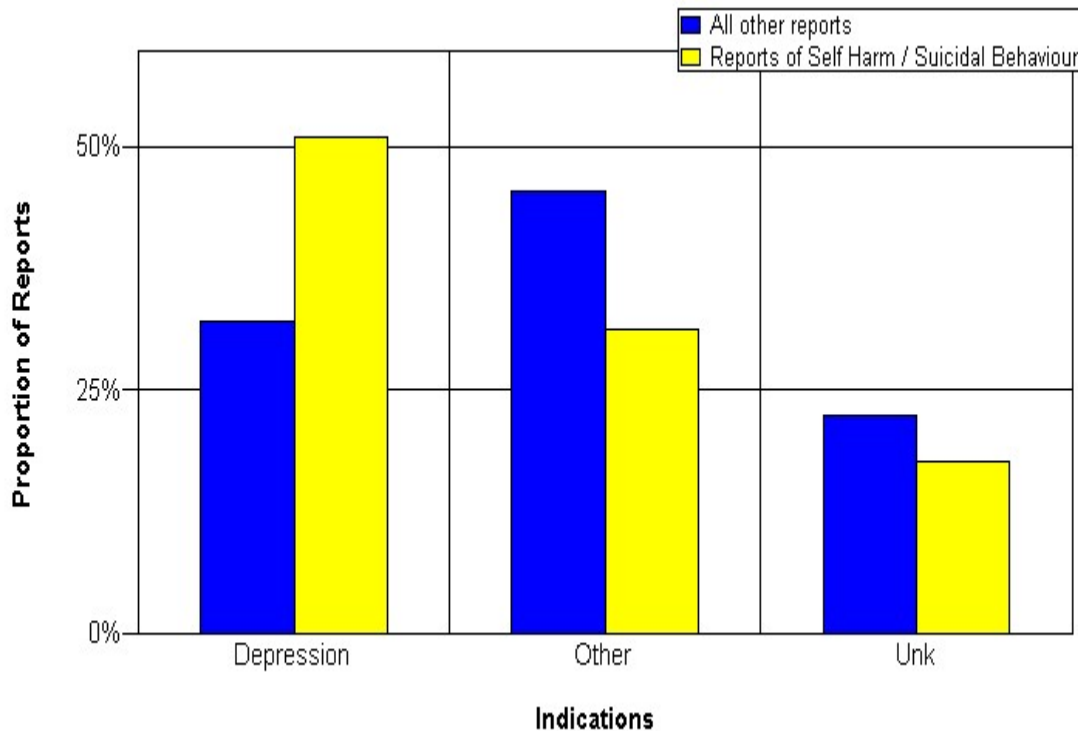
**12.2.2.3. Indication**

For both the HCP-confirmed reports (Figure 12.15) and those received from consumers (Figure 12.16), a relatively higher proportion of patients in the self-harm/suicidal behaviour group had received paroxetine for the treatment of depression (or depression plus other indications). In 52.0% (n = 39) of reports received from a HCP the patient was receiving paroxetine for depression (or depression plus other indications), with 33.0% (n = 25) having an unknown indication and 15.0% (n = 11) another indication. This compares to 45.0% (n = 399) of patients in the "other events" dataset with an indication of depression, 31.0% (n = 275) having an unknown indication and 25.0% (n = 222) with another indication. Similarly, in 51.0% (n = 26) of reports received from consumers the patient was receiving paroxetine for the treatment of depression, with 18.0% (n = 9) having an unknown indication and 31.0% (n = 16) another indication, compared to 32.0% (n = 113) of patients in the "other events" dataset with an indication of depression, 22.0% (n = 79) having an unknown indication and 46.0% (n = 160) with another indication.

**Figure 12.15 Indication of depression – reports received from healthcare professionals**



**Figure 12.16 Indication of depression – reports received from consumers**



The proportion of paediatric patients who were receiving paroxetine for OCD (or OCD plus other indications) was lower in the self-harm/suicidal behaviour dataset with 2.7% (n = 2) of HCP reports and 5.9% (n = 3) of consumer reports documenting an indication of OCD compared to 11.3% (n = 101) and 10.5% (n = 37), respectively, of HCP and consumer reports in the "other events" dataset.

**12.2.2.4. 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 a higher proportion of reports in the self-harm/suicidal behaviour dataset noting such a history compared to the "other events" dataset. The pattern was similar for both HCP and consumer reports, with 4.0% (n = 3) of HCP reports and 3.9% (n = 2) of consumer reports documenting self-harm/suicidal behaviour prior to the use of paroxetine, compared to 1.1% (n = 10) and 0.9% (n = 3) of HCP and consumer reports, respectively, in the "other events" dataset.

**12.2.2.5. Concomitant pharmacotherapies**

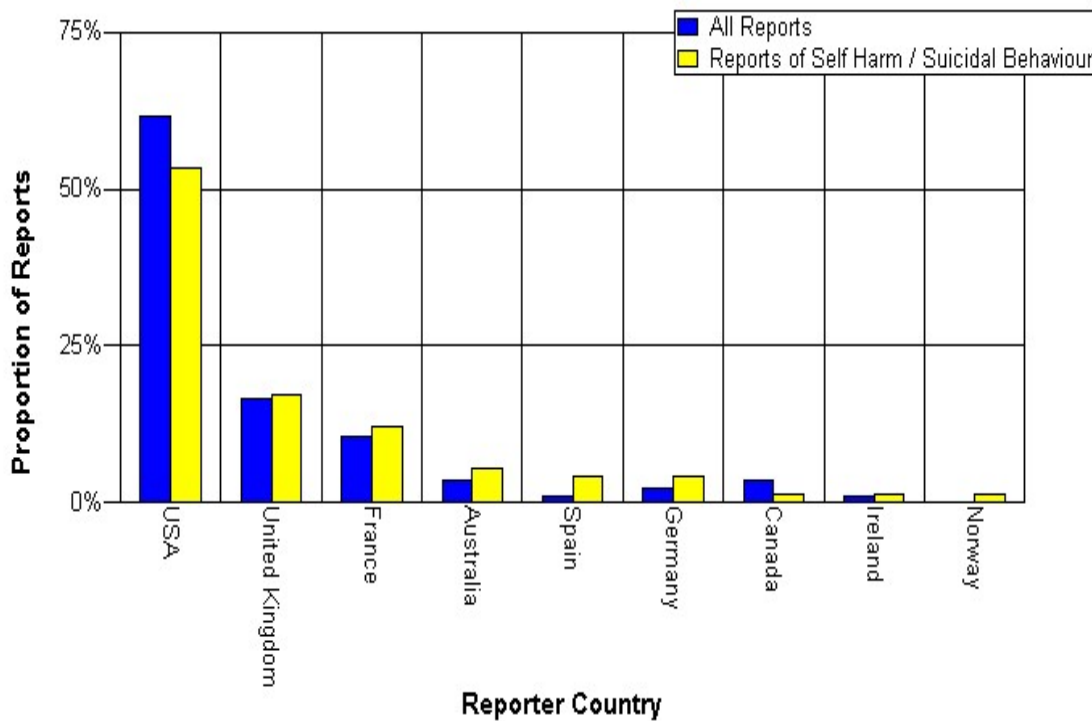
Differences in the pattern of psychotropic medication use was less marked in the paediatric population than the adult population, with 30.7% (n = 23) of HCP reports and 23.5% (n = 12) of consumer reports in the self-harm/suicidal behaviour paediatric dataset having received concomitant psychotropic medication compared to 24.8% (n = 222) and 25.9% (n = 91) of reports in the "other events" dataset.



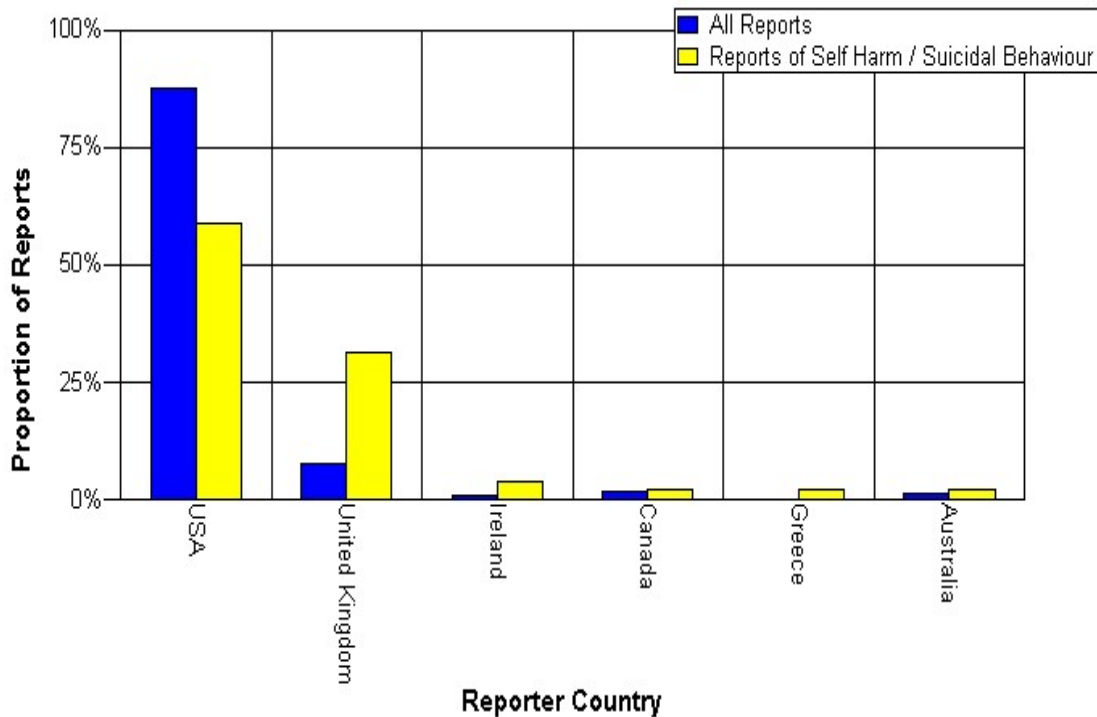
**12.2.2.6. Country of origin**

Figure 12.17 (HCP reports) and Figure 12.18 (consumer reports) provide an analysis of reporter country distribution for the paediatric self-harm/suicidal behaviour dataset compared with reports of all events. The graphs include those countries which reported more than one case of self-harm/suicidal behaviour. As was observed for the corresponding adult dataset, the reports received from consumers in the UK accounted for a relatively high proportion of reports of self-harm/suicidal behaviour (31.4%) when compared with the proportion of all reports occurring in the UK (7.7%). This observation is likely to be accounted for by increased reporting stimulated by media attention, in particular a series of BBC Panorama programmes televised in the UK in 2002 and 2003. Since the number of paediatric cases was smaller than the number of adult cases, with only 126 paediatric self-harm/suicidal behaviour cases in total, the number of cases reported by the remaining countries was too small to know whether any observed differences were significant. The graphs include those countries which reported more than one case of self-harm/suicidal behaviour.

**Figure 12.17 Distribution by country – reports received from healthcare professionals**



**Figure 12.18 Distribution by country – reports received from consumers**



**12.2.2.7. Time-to-onset and daily dose**

In order to review the time-to-onset and daily dose of paroxetine at the time of the event in the paediatric reports of self-harm/suicidal behaviour, the 15 completed suicide cases (11 HCP reports, 4 consumer reports) were manually reviewed. Of the 15 cases reviewed, in one report (received from a HCP) the suicide occurred after therapy with paroxetine had been discontinued, in two of the reports (both HCP reports) it was not specified if the patient had received paroxetine prior to the suicide, and in five reports (2 HCP reports, 3 consumer 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 (all HCP reports), within the second month in a single consumer report, within the third month in two HCP reports and in the fourth month in the final HCP report. The dosage at the time of the event was up to 20 mg daily in six of the seven reports where dose was provided. No significant differences were seen between reports received by HCPs or those received by consumers.

### **12.2.3. Summary of potential risk factors for self-harm/suicidal behaviour**

The review of post-marketing reports of self-harm/suicidal behaviour in adult and paediatric patients receiving paroxetine submitted by GSK on 01 September 2003, in which all reports were evaluated together, irrespective of report source, 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. The UK and Germany were found to be the source of relatively more reports of self-harm/suicidal behaviour than other countries when compared with the proportion of reports occurring in that country. In adults, 69% of the events were reported to have occurred within the first month of paroxetine therapy and 73% 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.

Upon reanalysis of the data, no significant differences were seen between those reports received from healthcare professionals and those received from consumers or other non-medically validated sources. Separation of the reports into healthcare professional and consumer reports has led to a reduction in the number of reports in each of the individual risk factor analyses, however, the same trends are still apparent and the conclusions provided by GSK in the initial response document have not changed.

### **12.3. Results of analysis for potential risk factors for withdrawal reactions**

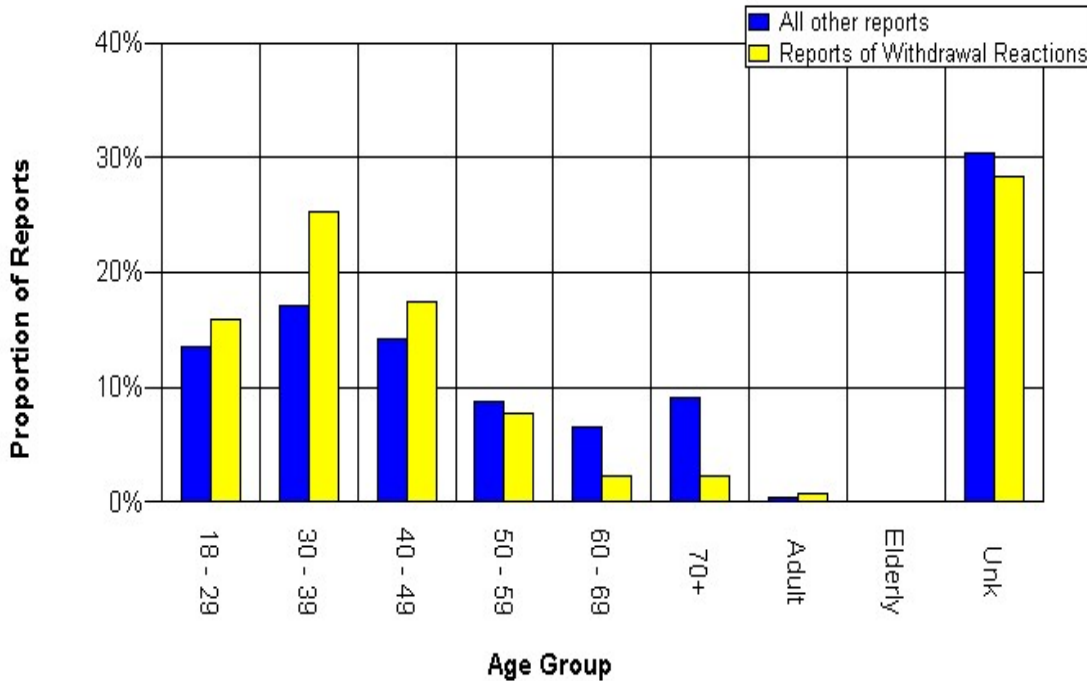
#### **12.3.1. Withdrawal reactions - adults and patients of unspecified age**

GSK received 3,777 reports of withdrawal reactions in adults and patients of unspecified age up to 31 May 2003. Of these reports 2,011 (53.0%) were received from HCPs and 1,766 (47.0%) were received from consumers or other non-medically validated sources. GSK received 37,692 reports of "other events" in adults or patients of unspecified age in the same period, of which 25,954 (69.0%) were received from HCPs and 11,738 (31.0%) were received from consumers. In this analysis of risk factors, the dataset of 2,011 reports from HCPs documenting withdrawal reactions is compared with the 25,954 HCP-confirmed reports of "other events". Similarly, the 1,766 consumer reports of withdrawal reactions are compared with the 11,738 consumer reports of "other events".

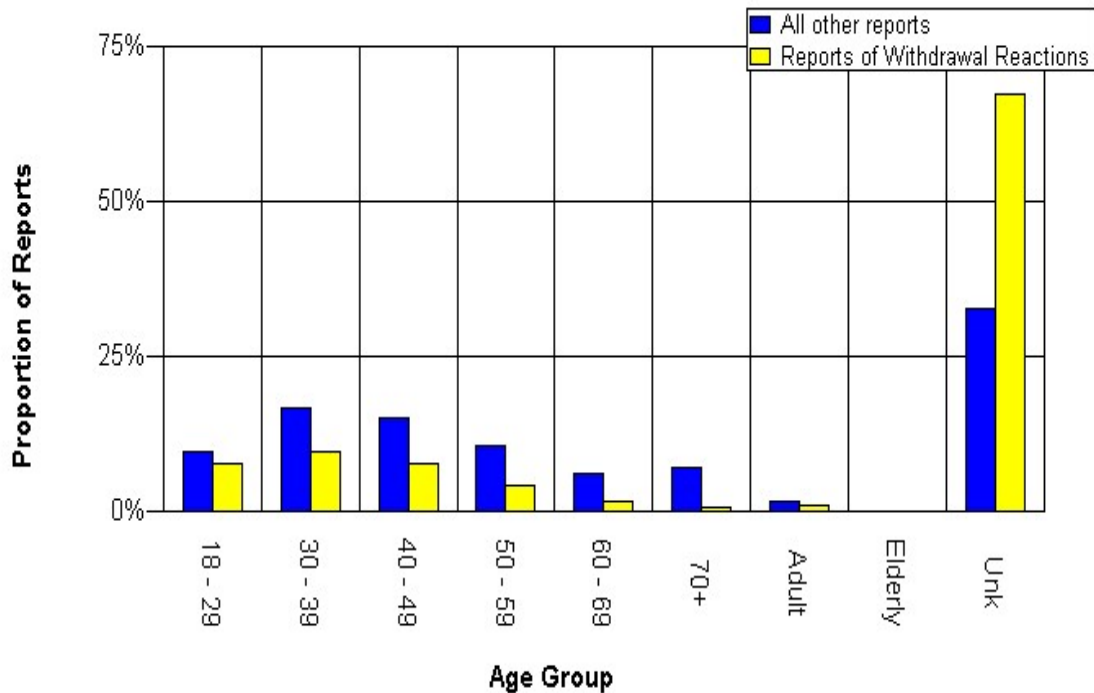
**12.3.1.1. Age distribution**

The age distribution of the adult dataset is presented in [Figure 12.19](#) (HCP confirmed reports) and [Figure 12.20](#) (consumer reports). Note: the age groups "adult" and "elderly" are used when a specific age was not provided but when it was known from the reporter's description that the category was appropriate. [Figure 12.19](#) shows that withdrawal reactions were more frequently reported in the 30-39 age group than "other events" when examining reports received from HCPs, with 25.4% (n = 510) reports of withdrawal reactions occurring in this age group compared to 17.1% (n = 4,439) of reports in the "other events" dataset. No specific age group appears to be prominent when comparing the withdrawal reactions dataset with the "other events" dataset for the consumer reports ([Figure 12.20](#)), however, it should be noted that in a large proportion of the reports of withdrawal reactions received from consumers the patient's age was unspecified. It seems unlikely that patients in the 30-39 years age band would have a different inherent susceptibility to withdrawal reactions than other adults.

**Figure 12.19 Age distribution – reports received from healthcare professionals**



**Figure 12.20 Age distribution – reports received from consumers**



**12.3.1.2. Gender**

The withdrawal reactions dataset included a slightly higher proportion of female patients compared to the dataset of "other events" when examining both the HCP and consumer reports. Of the 2,011 HCP reports of withdrawal reactions, 64.4% were female (n = 1,295), 21.9% were male (n = 441) and 13.7% (n = 275) were of unspecified gender, compared to 60.9% (n = 15,797) females, 25% (n = 6,496) males and 14.1% (n = 3,661) unspecified gender in the "other events" dataset. Similarly, of the 1,766 consumer reports of withdrawal reactions, 71.0% (n = 1,253) were female 23.2% (n = 409) were male and 5.9% (n = 104) were of unspecified gender. This compares to 65.5% (n = 7,684) female, 30.6% (n = 3,591) male and 3.9% (n = 463) unspecified gender in the "other events" dataset.

**12.3.1.3. Indication**

The proportion of patients who were receiving paroxetine for depression (or depression plus other indications) was slightly higher in the withdrawal reactions dataset compared to the "other events" dataset when examining the HCP reports, with 61.3% (n = 1,233) of withdrawal reaction reports documenting an indication of depression, 29.3% (n = 589) having an unknown indication and 9.4% (n = 189) having another indication. This compares to 52.6% (n = 13,647) of patients in the "other events" dataset documenting an indication of depression, 36.4% (n = 9,447) an unknown indication and 11.0% (n = 2,860) another indication. In contrast, for the consumer reports the proportion of patients receiving paroxetine for depression is lower in the withdrawal reactions dataset than in the "other events" dataset, with 23.9% (n = 422) of withdrawal reaction reports

documenting an indication of depression, 61.5% (n = 1,086) having an unknown indication and 14.6% (n = 258) another indication. This compares to 41.1% (n = 4,829) of patients in the "other events" dataset documenting an indication of depression, 32.6% (n = 3,829) documenting an unknown indication and 26.2% (n = 3,080) another indication.

The proportion of patients who were receiving paroxetine for OCD (or OCD plus other indications) was similar in both datasets for both HCP and consumer reports, with 1.9% (n = 38) of HCP reports and 1.7% (n = 30) of consumer reports documenting an indication of OCD compared to 2.1% (n = 539) and 3.7% (n = 432), respectively, in the HCP and consumer "other events" dataset.

#### **12.3.1.4. Concomitant pharmacotherapies**

In the withdrawal reactions dataset the proportion of patients who had received concomitant psychotropic medication was low with 16.7% (n = 335) of HCP reports and 8.2% (n = 145) of consumer reports documenting concomitant psychotropic medication, compared to 28.7% (n = 7,447) and 19.9% (n = 2,336), respectively, in the HCP and consumer "other events" dataset.

#### **12.3.1.5. Country of origin**

The analysis of reporter country distribution allowed a comparison of the proportion of all reported withdrawal reactions with the proportion of all events that arose in that country. [Figure 12.21](#) and [Figure 12.22](#), respectively, show the distribution of HCP and consumer reports by country. The graphs include those countries which reported more than one case of withdrawal reaction. [Figure 12.21](#) shows that the proportion of withdrawal reactions received from HCPs in the UK was considerably greater than the proportion of all events received in that country with 52.1% of all reports of withdrawal reactions coming from the UK and only 25.4% of all reports. The trend was much less marked for consumer reports ([Figure 12.22](#)), with 12.63% of withdrawal reaction reports coming from the UK and only 9.9% of all reports. This observation with the UK is believed to be a result of the publicity given to this type of event in this country. It should also be noted that the majority of all consumer reports (including reports of withdrawal reactions) came from the USA.

Figure 12.21 Distribution by country – reports received from healthcare professionals

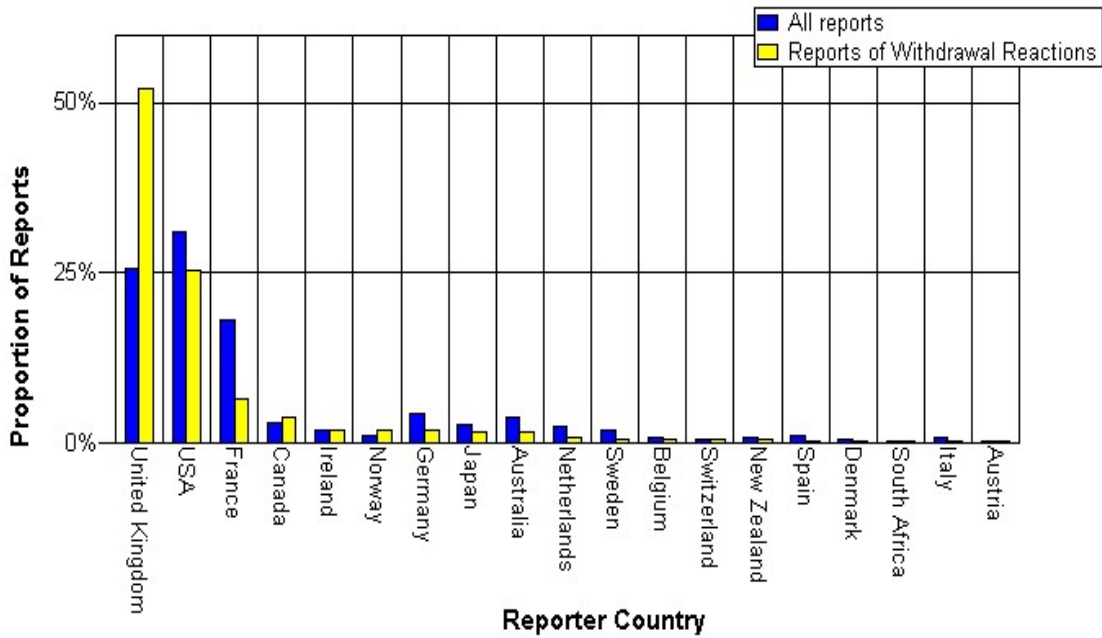
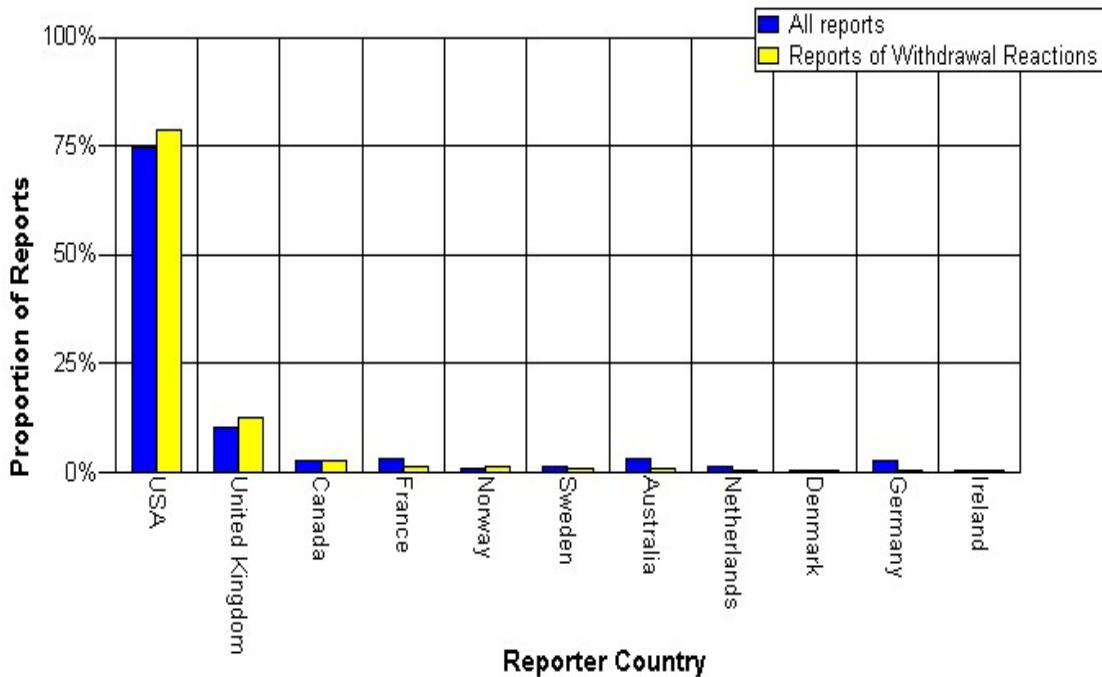


Figure 12.22 Distribution by country – reports received from consumers



### **12.3.2. Withdrawal reactions - paediatric patients**

GSK received 53 reports of withdrawal reactions in paediatric patients (up to and including 17 years of age) up to 31 May 2003. Of these reports 58.0% (n = 31) were received from HCPs and 42.0% (n = 22) were received from consumers or other non-medically validated sources. A total of 1,321 reports of "other events" in the same age group were received in the same time period of which 71.0% (n = 940) were received from HCPs and 29.0% (n = 381) from consumers. In this analysis of risk factors, the 31 reports of withdrawal reactions received from HCPs is compared with the 940 reports of "other events" received from HCPs. Likewise, the 22 reports of withdrawal reactions received from consumers are compared with the 381 reports of "other events" received from consumers. Given the relatively small number of reports in each of the withdrawal reaction datasets, care should be taken in the interpretation of these analyses.

#### **12.3.2.1. Age distribution**

The age distribution of the reports received from HCPs and consumers in the paediatric dataset is presented in [Figure 12.23](#) (HCP reports) and [Figure 12.24](#) (consumer reports). Note: the age groups "child" and "teenager" are categories used when a specific age was not provided but when it was known from the reporters 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. No obvious differences are apparent between the age profiles for the reports documenting withdrawal reactions versus those for all "other events".



Figure 12.23 Age distribution – reports received from healthcare professionals

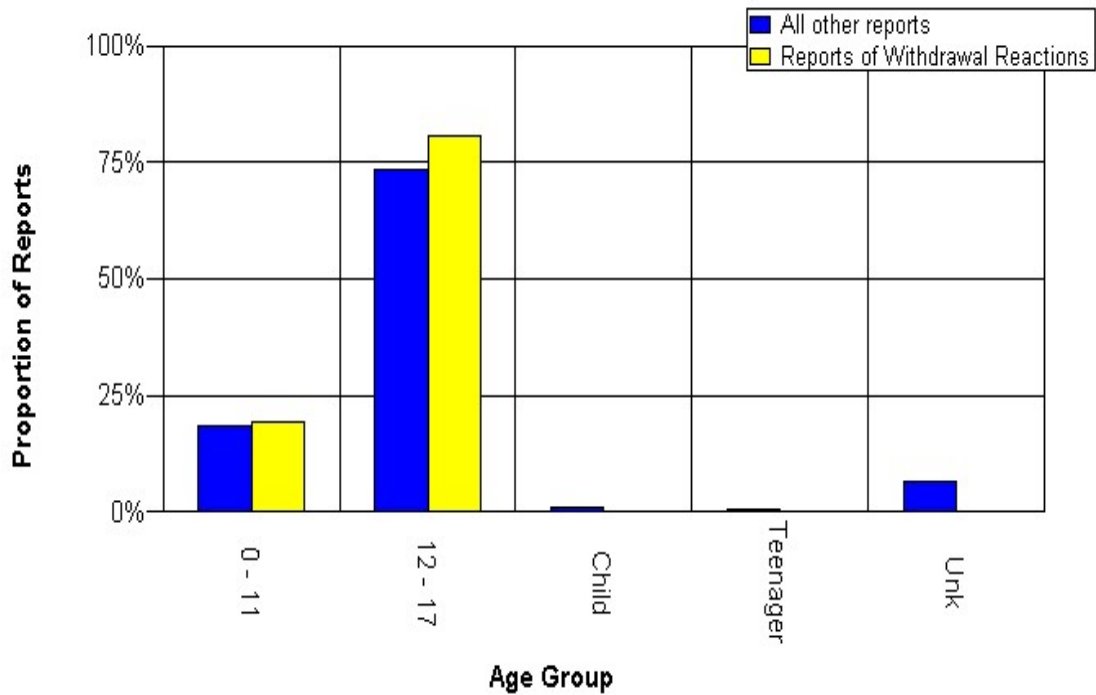
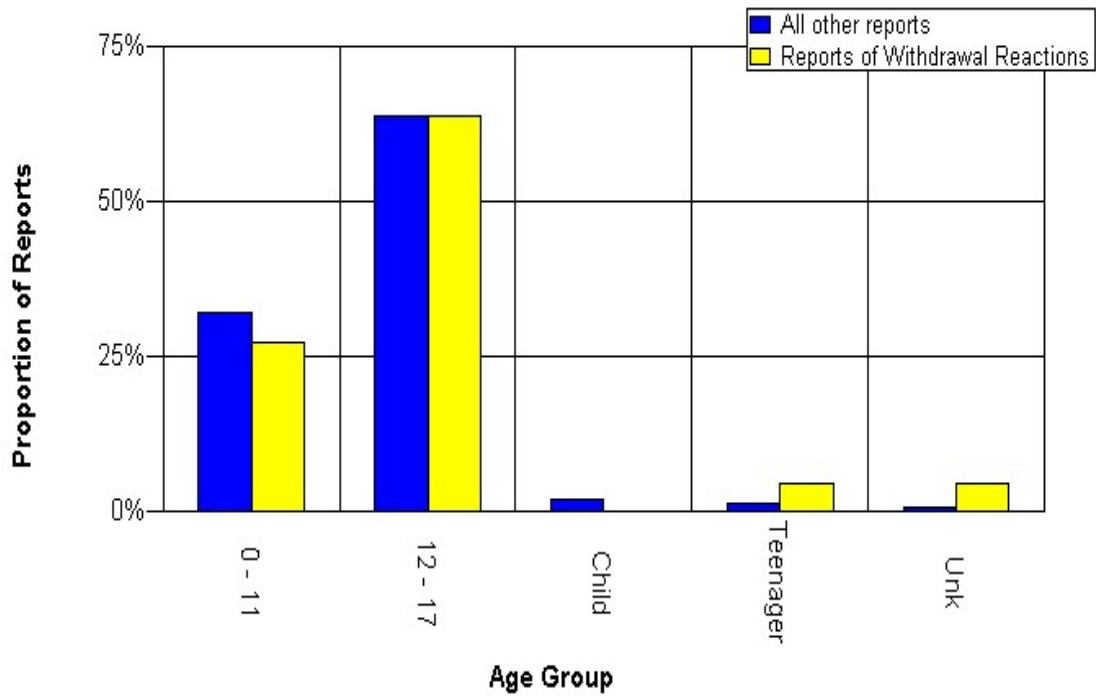


Figure 12.24 Age distribution – reports received from consumers



**12.3.2.2. Gender**

The gender split between the withdrawal reactions dataset and the "other events" dataset was very similar when examining the HCP reports, with 61.3% (n = 19) of reported withdrawal reactions occurring in females, and 38.7% (n = 12) occurring in males, compared to 56.0% (n = 526) of "other events" occurring in females, 36.2% (n = 340) in males, and 7.9% (n = 74) occurring in patients of unspecified gender. A slightly higher proportion of male patients with withdrawal reactions, however, were observed upon examination of the consumer reports, with 50.0% (n = 11) of withdrawal reactions occurring in males, 45.5% (n = 10) in females, and 4.6% (n = 1) in patients of unspecified gender, compared to 45.7% (n = 174) of "other events" occurring in males, 51.2% (n = 195) in females and 3.2% (n = 12) in patients of unspecified gender.

**12.3.2.3. Indication**

The differences between the proportion of patients who were receiving paroxetine for depression (or depression plus other indications) in the withdrawal reactions and the "other events" dataset were small. In 48.4% (n = 15) of reports received from a HCP and 27.3% (n = 6) of reports received from consumers the patient was reported to be receiving paroxetine for the treatment of depression (or depression plus other indications). This compares to 45.0% (n = 423) of HCP reports and 34.9% (n = 133) of consumer reports in the "other events" dataset. The proportion of patients receiving paroxetine for OCD (or OCD plus other indications) was also similar in both datasets, with 12.9% (n = 4) of HCP reports and 9.1% (n = 2) of consumer reports documenting an indication of OCD, compared to 10.5% (n = 99) and 10.0% (n = 38), respectively, of HCP and consumer reports in the "other events" dataset.

**12.3.2.4. Concomitant pharmacotherapies**

As with the adult population, in the paediatric withdrawal reactions dataset the proportion of patients who had received concomitant psychotropic medication was low, with 19.4% (n = 6) of HCP reports and 9.0% (n = 2) of consumer reports documenting concomitant psychotropic medication, compared to 25.4% (n = 239) and 26.5% (n = 101), respectively, of HCP and consumer reports in the "other events" dataset.

**12.3.2.5. Country of Origin**

The analysis of reporter country distribution indicated that the UK was the source of relatively more reports of withdrawal reactions than other countries when compared with the proportion of reports of all events occurring in that country, as shown in [Figure 12.25](#) (HCP reports) and [Figure 12.26](#) (consumer reports). The graphs include all countries which reported a case of withdrawal reactions in a paediatric patient.

Figure 12.25 Distribution by country – reports received from healthcare professionals

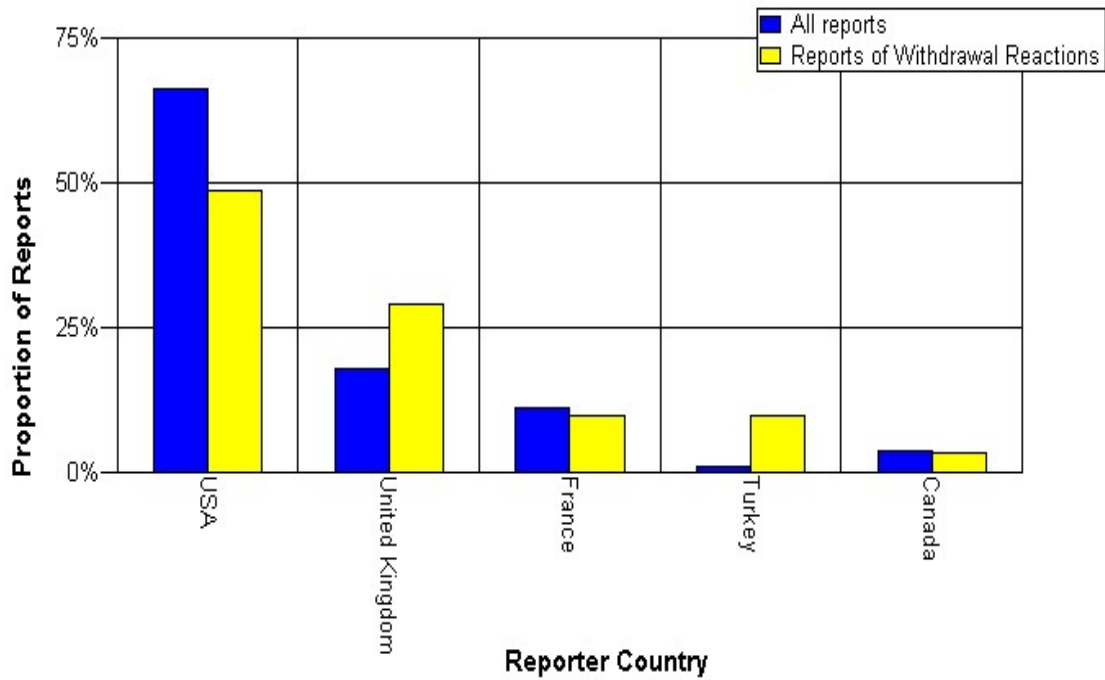
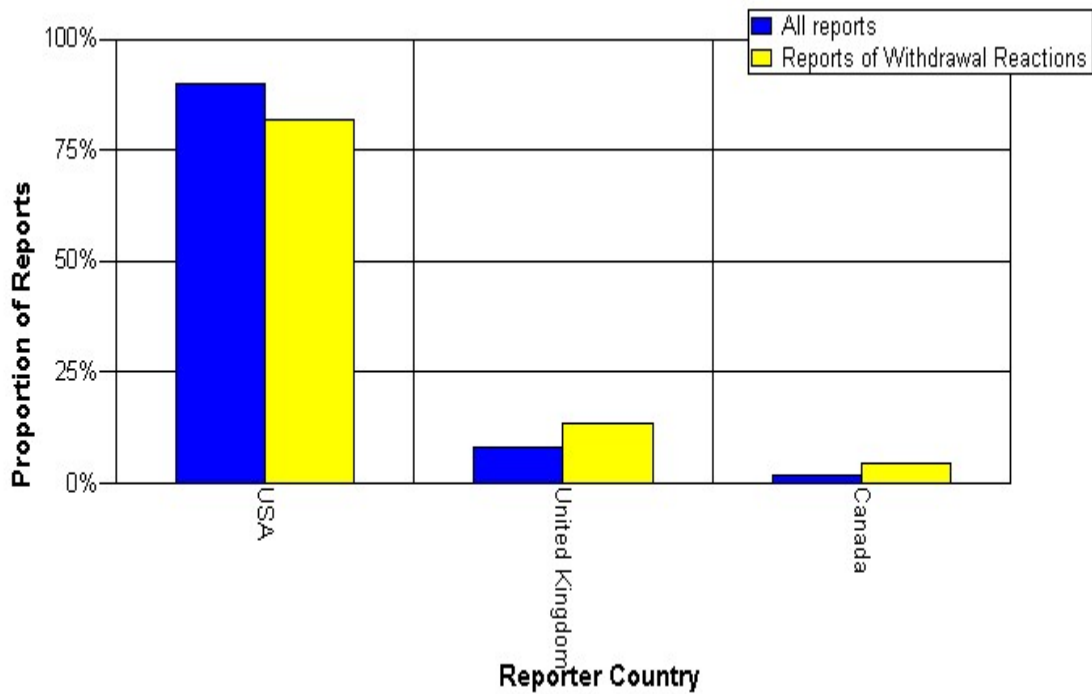


Figure 12.26 Distribution by country – reports received from consumers



### **12.3.3. Summary of potential risk factors for withdrawal reactions**

The review of post-marketing reports of withdrawal reactions in adult and paediatric patients receiving paroxetine submitted by GSK on 01 September 2003, in which all reports of withdrawal reactions were evaluated together, irrespective of report source, revealed that no particular age group were reported to be involved in withdrawal reactions compared to other events. Relatively more adult females were reported to have experienced withdrawal reactions compared to the proportion of females who experienced other events but this difference was not reflected in paediatric patients. The proportion of patients who were treated for depression was slightly lower in the withdrawal reactions dataset than the "other events" dataset but no such differences were observed in the paediatric dataset. No difference was observed in the proportion of patients treated for OCD. In both adult and paediatric patients the proportion of patients who had received concomitant psychotropic medications was lower for patients who had experienced withdrawal reactions than those who had experienced "other events". The UK was found to be the source of relatively more reports of withdrawal reactions than other countries when compared with the proportion of reports occurring in that country.

In the new analysis reported here, no major differences were seen between those reports of withdrawal reactions received from healthcare professionals and those received from consumers or other non-medically validated sources. Separation of the reports into healthcare professional and consumer reports has led to a reduction in the number of adverse events in each of the individual analyses of risk factors, however, the same trends are still apparent and the conclusions provided by GSK in the initial response document have not changed.