8. QUESTION 8

Consider the need for specific advice in the SPC about what action should be taken if a patient develops akathisia or suicidal behaviour whilst on treatment.

Response

8.1. Introduction

In principle there are several actions possible regarding paroxetine treatment if a patient develops akathisia or suicidal behaviour whilst receiving the drug. The patient could be withdrawn from the drug, or the dose could be reduced, maintained or increased. An evidence-based approach will be taken to answering this question, however evidence-based implies general recommendations resulting from observing a population, and specific advice is always required for individuals. Hence recommendations can be made as to what would be appropriate for most people, but there should be recognition that one rule can't fit all, and that the physician's judgement on what is best for the individual patient at a particular time is what should determine the action that is taken.

A critical question in deciding the course of action to take is whether the event is considered to be caused by paroxetine. If so, discontinuation of treatment seems in order. However, the available evidence suggests that paroxetine does not induce suicidal behaviour in adults. Indeed the evidence included in this review from patients with suicidal ideation at the start of treatment indicate that paroxetine reduces the incidence of possibly suicide related events. With regards to akathisia, data from the clinical trials database indicate that this specific event was reported at a low frequency in adults, but was described more frequently in the paroxetine-treated patients compared with placebo recipients. The proposed SPC wording submitted by GSK in 01 September 2003 includes reference to akathisia within Section 4.8, Undesirable Effects.

The data regarding the risk of suicidal behaviour and akathisia in patients treated with paroxetine, and a further discussion of the management of patients presenting with such events during therapy, are presented in sections 8.1.1 (suicidal behaviour) and 8.1.2 (akathisia) below.

8.1.1. Suicidal behaviour

Review of the paroxetine clinical trial database does not support the hypothesis that paroxetine induces suicidal behaviour in adults.

In adult placebo-controlled studies the incidence of possibly suicide-related AEs was no higher in patients treated with paroxetine (0.8%, 66/8481) than in patients treated with placebo (0.9%, 55/5808). Indeed evidence suggests that paroxetine may reduce the risk of suicidal behaviour in adults. In patients with suicidal ideation at baseline, significantly less patients experienced possibly suicide-related AEs while on paroxetine (3.4%, 15/444) than on placebo treatment (7.2%, 21/291), (odds ratio 0.45, 95% CI [0.23, 0.89]; p=0.023). Patients who did not have suicidal ideation at baseline or for whom baseline

suicidal ideation was not assessed, reported possibly suicide-related AEs at similar incidences in the paroxetine and placebo groups, 0.6% (51/8037) and 0.6% (34/5517), respectively. Further, significantly less patients who did not have suicidal ideation at baseline, reported emergent suicidal ideation (assessed by MADRS item 10) when treated with paroxetine (1.8%, 44/2387) than with placebo (2.8%, 52/1834), (odds ratio 0.64, 95% CI [0.43, 0.97], p=0.03).

In addition, in active control studies, a lower percentage of patients experienced possibly suicide-related events on paroxetine than on treatment with an active comparator (paroxetine 0.8% (55/6522), comparator 1.3% (63/4969; odds ratio 0.66, 95% CI [0.46. 0.95], p=0.031), and less patients with suicidal ideation at baseline experienced possibly suicide-related AEs while on paroxetine than on active comparator treatment; 1.9% (14/735) vs 2.6% (15/582), respectively, (although this difference was not statistically significant.

There is a suggestion of an increased risk of suicidal behaviour in young adults receiving paroxetine (see response to Question 5).. However, in young adults aged 18-29, the incidence of possibly suicide-related events in placebo-controlled trials was not significantly greater in patients on paroxetine (1.8%, 31/1727) than on placebo (1.4%, 17/1204), (odds ratio 1.28, 95%CI [0.70, 2.32], p=0.46), and in active control studies was significantly less than on comparator treatment (paroxetine 1.0%, 10/969; comparator 2.6%, 20/779; odds ratio 0.40, 95% CI [0.18, 0.85], p=0.016).

Even in children and adolescents there is not consistent, compelling evidence of an excess risk of suicidal behaviour with paroxetine treatment. A signal of more suicide-related events was observed, and emergent suicidal ideation, as assessed by HAMD item 3 change, appeared greater with paroxetine than placebo treatment (paroxetine 3.2% (5/154), placebo 0.7% (1/146), odds ratio 4.87, 95%CI [0.56, 42.16], p=0.22). However, there is contradictory evidence from assessment of emergent suicidal ideation as assessed by MADRS item 10 change. In the studies employing the MADRS rating scale, emergent suicidal ideation was less on paroxetine than on placebo (4.9% vs 11.1%, odds ratio 0.41, 95% CI [0.10, 1.61], p=0.20).

In conclusion, there is no evidence to suggest that paroxetine increases the risk of suicidal behaviour in adults, but there is evidence that in patients who have suicidal thoughts, treatment with paroxetine results in significantly less possibly suicide-related events than treatment with placebo. Consequently, when considering what action to take for a patient who develops suicidal behaviour whilst on treatment, it should be borne in mind that there is no evidence to support stopping paroxetine. The potentially dangerous consequences of the patient's condition worsening while a replacement therapy is introduced is also a consideration.

8.1.2. Akathisia

It has been proposed that SSRIs, such as paroxetine, may induce agitation or akathisia-like events soon after therapy is started and that the distress this causes in an already vulnerable group leads to suicidal behaviour [Healy, 1994]. However this suggestion is

not supported by the findings from the adult clinical studies with paroxetine or the post-marketing adverse event data.

The occurrence of agitation occurring early in treatment prior to possibly suicide-related adverse events was investigated. Early treatment emergent agitation was defined as a HAM-D Item 9 score of ≥ 2 within 28 days of starting treatment in patients with Item 9 scores of 0 or 1 at baseline and excluding treatment emergent agitation observed after a possibly suicide-related event. In adult placebo-controlled trials, the incidence of 4.0% (335/8481) in the paroxetine group and 4.2% (246/5808) in the placebo-treated patients were similar.In the subgroup of paroxetine-treated patients with early treatment emergent agitation (n=335), only a very low proportion subsequently experienced possibly suicide-related AEs, (2/335 on paroxetine vs 0/246 on placebo).

Another way of investigating this proposed mechanism is to compare the incidence of paroxetine and placebo treated patients who had treatment emergent agitation as defined by the occurrence after starting study medication of an adverse experience that coded to the preferred term "agitation", excluding those that occurred after a possibly suicide-related event. The incidences of patients with treatment emergent agitation by this definition were 1.9% (160/8481) and 1.9% (113/5808) for paroxetine and placebo, respectively. Of those patients with treatment emergent agitation, only 2 patients in the paroxetine group and 1 in the placebo group experienced possibly suicide-related AEs.

In the clinical dictionary used for coding adverse events reported in paroxetine clinical studies, adverse event verbatim terms relating specifically to akathisia generally map to the dictionary preferred term of hyperkinesia, as akathisia is classified as a movement disorder. Therefore, a search of the database of adult clinical studies has been conducted for adverse event verbatim terms containing the text string "akathis". In adult placebo-controlled studies, the overall incidence of such events on-therapy was 0.2% (17/8481) in the paroxetine group and 0.1% (3/5808) in the placebo group, with an odds ratio of 3.89 (95% CI 1.14, 13.27; P value 0.021), (Data Source: Appendix 1, Table 9.01). Only one of the 17 paroxetine-treated patients experienced a subsequent possibly suicide-related AE.

The incidences of AEs relating to akathisia occurring on-therapy in adult active controlled trials were 0.3% (17/6522) for the paroxetine group and 0.3% (17/4969) for the comparator group (Data Source: Appendix 1, Table 9.03). Of those patients in whom an AE relating to akathisia were reported, two individuals treated with paroxetine subsequently experienced a possibly suicide-related AE (of which one was the same patient described in the previous paragraph regarding the dataset for placebo-controlled studies).

The post-marketing experience of reports of akathisia also warrant discussion here. In response to a regulatory authority enquiry from the UK Medicines Control Agency (now MHRA), in April 2002 GSK completed a detailed evaluation of all reports of akathisia for paroxetine retrieved from the GSK Clinical Safety database (which includes all reports received worldwide from spontaneous notifications, post-marketing surveillance studies and the serious adverse event reports from clinical studies). A total of 123 reports were identified in which an AE of akathisia or possible akathisia was documented, of

which 117 (95%) came from spontaneous notifications. Of these 123 reports, in four cases the onset of suicidal tendency or suicidal ideation was reported, however, none of these patients attempted suicide. A copy of GSK's detailed evaluation submitted to the UK authority is available upon request.

In summary, therefore, in the adult clinical trial population adverse events specifically relating to akathisia were reported at a low frequency, but the incidence was higher in the paroxetine-treated patients (0.2%) compared with placebo recipients (0.1%) and this difference achieved statistical significance. The incidence of akathisia in patients treated with comparator medication was the same as reported for paroxetine. In the post-marketing setting, reports of akathisia have been received very rarely in the context of the extensive patient exposure. The available data do not support the hypothesis that the development of akathisia (or agitation) result in the precipitation of suicidal behaviour in adult patients.

With respect to paediatric patients, in paroxetine paediatric placebo-controlled trials, early (within 28 days of starting treatment) treatment emergent agitation (as defined by HAM-D Item 9 changes described above) was experienced by 37/738 (5.0%) paediatric patients treated with paroxetine, and by 41/647 (6.3%) placebo treated patients. Only one patient with early treatment emergent agitation in each treatment group, i.e. 1/37 paroxetine and 1/41 placebo-treated patient, experienced possibly suicide-related AEs during study. Similarly, there was only one patient in the paroxetine paediatric clinical trial programme that reported a possibly suicide-related AE after reporting an AE of treatment emergent agitation.

A search of the database of paediatric placebo controlled trials has also been conducted for AE verbatim terms containing the text string "akathis". The incidence of such events on-therapy was identical for the paroxetine and placebo groups, with 0.5% (4/738) paroxetine-recipients and 0.5% (3/647) placebo patients experiencing an akathisia-related AE, (Data Source: Appendix 1, Table 9.05). None of these paediatric patients reported with an AE term relating to akathisia experienced a subsequent possibly suicide-related AE. These data certainly do not support the theory that, in paediatric patients, paroxetine induces suicidal behaviour as a result of producing akathisia or agitation.

Turning now to the advice that might be provided regarding the management of the rare adult patient who may develop akathisia-like symptoms, it is important to recognise that akathisia has also been described in association with a broad range of other psychotropic medications, including neuroleptics, tricyclics, monoamine oxidase inhibitors and other SSRIs. Additionally, as described in the DSM-IV research criteria for neuroleptic-induced akathisia, individuals with depressive episodes, manic episodes, generalised anxiety disorder, schizophrenia and other psychotic disorders, attention-deficit/hyperactivity disorder, dementia, delirium, substance intoxication or substance withdrawal may also display psychiatric symptoms which are difficult to distinguish from akathisia. Hence, establishing whether paroxetine (or a concurrent medication or underlying psychiatric disorder) is the most likely cause of the onset of akathisia-like symptoms in any individual patient may not be straightforward. However, given that an association between the onset of akathisia or agitation and the development of suicidal behaviour is not supported by the data on paroxetine, there is not an absolute need for

therapy to be immediately withdrawn. Rather, the physician will need to consider the range of management options available in the context of the severity of the akathisia symptoms and the potential benefit the patient may derive from continued therapy.

8.1.3. Conclusion

There is no compelling evidence that adult patients are more likely to develop suicidal behaviour as a result of treatment with paroxetine than placebo. On that basis there is no need for specific advice regarding paroxetine use in the SmPC (Summary of product Characteristics) about what action to take if a patient develops suicide-related events whilst on treatment. We have already proposed disease related wording in section 4.4 of the SmPC concerning close monitoring of patients generally who have depression or other psychiatric disorders to guide the prescriber. We believe this appropriate and adequate clinical advice if a patient develops suicidal behaviour on treatment. However, given the recent publicity and lay-press comments, particularly regarding paroxetine and suicidal behaviour, it may be useful to include a statement in the SmPC reflecting the first sentence of this conclusion, i.e. "There is no compelling evidence that adult patients are more likely to develop suicidal behaviour as a result of treatment with paroxetine than placebo". Physicians would then be able to use their judgement for the individual cases presenting, with a range of possibilities open to them.

The available data suggest that paroxetine may rarely be associated with the development of akathisia-like symptoms in adult patients. Akathisia is included in Section 4.8 of the SPC wording originally proposed by GSK in its submission of 01 September 2003 and the subsequent draft SPC proposed by CPMP. No additional guidance regarding the management of patients presenting with akathisia-like symptoms is considered appropriate, as the prescribing physician should consider each individual patient on a case-by-case basis.

8.2. References

Healy D. The fluoxetine and suicide controversy. A review of the evidence. *CNS Drugs* 1994; 1(3): 223-231.