4. QUESTION 4: POSSIBLE MECHANISMS TO INDUCE SUICIDAL BEHAVIOUR

Discussion of mechanism by which paroxetine may induce suicidal behaviour in

- *Children/adolescents*
- *Adults*

Response

4.1. Introduction

Clinical depression is a major public health problem that can lead to suicidal behaviour (i.e. ideation, attempts, and completed suicide). There is a considerable body of population research that has confirmed that major depression increases the risk of suicidal behaviour compared to the risk in people without depression [Kessler, 1999][Weissman, 1999][Angst, 1992][Beautrais, 1996].

Suicidal behaviour is very complex with several factors working simultaneously. These risk factors vary with age, gender and ethnicity, and may even change over time. Males are 4 times more likely to complete suicide, while women report attempting suicide 2 to 3 times more often than males [National Institute of Mental Health, 2001].

In the United States, the elderly and young adults have the highest rates of completed suicide [National Institute of Mental Health, 2001]. Several types of adverse life events in combination with other risk factors, such as depression, can lead to suicide [National Institute of Mental Health, 2001]. Other known risk factors for suicidal behaviour are: prior suicide attempt; family history of mental disorder or substance abuse; family history of suicide; family violence, including physical or sexual abuse; firearms in the home; incarceration; and exposure to the suicidal behaviour of others, including family members, peers, or even in the media [National Institute of Mental Health, 2001]. After the elderly, adolescents and young adults have the next highest risk of suicide and suicidal behaviour. According to the U.S. Surgeon General, for young people 15-24 years old, suicide is the third leading cause of death, behind unintentional injury and homicide [Office of the Assistant Secretary for Health, 1999]. In 1996, more teenagers and young adults died of suicide than from cancer, heart disease, AIDS, birth defects, stroke, pneumonia and influenza, and chronic lung disease combined. The rate of completed suicide appears to increase throughout adolescence and young adulthood. For children aged 10-14, the rate was 1.6/100,000, the rate for children aged 15-19 was 9.7 per 100,000, and the rate for young people aged 20-24 was 14.5/100,000 [Office of the Assistant Secretary for Health, 1999].

There is evidence that alterations in neurotransmitters such as serotonin are associated with the risk for suicide [Mann, 1999]. Diminished levels of this brain chemical have been found in patients with depression, impulsive disorders, a history of violent suicide attempts, and also in post-mortem brains of suicide victims.

There has been a long debate concerning treatment with SSRIs and their possible link to suicidality [Teicher, 1990]. Several biological models have been proposed to explain a possible link between SSRIs and suicidal behaviour. One hypothesis is that the acute effects of SSRI treatment include a compensatory decrease in 5-HT neuronal firing, which can lead to suicidality in certain vulnerable individuals [King, 1994]. Another theory is that SSRIs 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]. A recent review concluded, however, that akathisia cannot be linked unequivocally to suicidal behaviour [Hansen, 2001]. It has also been suggested that after depressed patients begin therapy, they recover their initiative and energy before their mood improves [Fava, 1991] and that this results in some acting upon or thinking about suicide during the period before mood improves. However, meta-analysis of controlled clinical data have not shown any evidence of an association between treatment-emergent suicidal ideation and fluoxetine [Beasley, 1991].

Most recently, a review of the FDA database investigated the rates of completed suicide for 48,277 treated depressed patients. Their conclusions were that there was "no difference in suicide risk between those receiving antidepressant and placebo, nor was there any difference between SSRIs and other antidepressants" [Khan, 2003].

4.2. Paroxetine and suicidal behaviour

4.2.1. Adults

Review of the paroxetine clinical trial database does not support the hypothesis that paroxetine induces suicidal behaviour in adults. (See responses to Questions 2 and 3).

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], and significantly less paroxetine than placebo-treated patients experienced AEs of self-harm (2.5% [11/444] vs 6.2% [18/291], odds ratio 0.39 (95% CI 0.18, 0.83), p=0.019). 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. Similarly, the incidence of self-harm in patients with baseline suicidal ideation or for whom baseline suicidal ideation was not assessed was similar in the two treatment groups; 0.5%(40/8037) and 0.4% (20/5517) for paroxetine and placebo patients, respectively.

In addition, a lower percentage of 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.

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. The occurrence of agitation prior to possibly suicide-related adverse events was investigated. In the subgroup of paroxetine-treated patients with early treatment emergent agitation (n=335, 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 those observed after a possibly suicide-related event), only a very low proportion subsequently experienced possibly suicide-related AEs, (2/335 on paroxetine vs 0/246 on placebo) [Appendix 3, Table 3.30]. Indeed, the observed incidences of early treatment emergent agitation (which excluded agitation that occurred after a possibly suicide-related event) of 4.0% (335/8481) in the paroxetine group and 4.2% (246/5808) in the placebo-treated patients were similar and also do not support this proposed mechanism for paroxetine.

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 [Appendix 3, Table 3.27].

In summary, no increased suicidality was seen in adults treated with paroxetine in clinical trials, and consequently discussion of the mechanism by which paroxetine may induce suicidal behaviour in adults is redundant. However, the agitation/akathisia suggestion has been investigated and is not supported by the paroxetine clinical trial data.

4.2.2. Children and Adolescents

In placebo-controlled studies in children and adolescents, there was no difference between the paroxetine and placebo groups in change from baseline of Item 3 of the HAM-D and Item 10 of the MADRS (the items relating to suicidality) and no conclusive evidence of emergent suicidal ideation (based on Item 3 of the HAM-D) in the paroxetine treatment group compared to the placebo group. However, the proportion of paroxetine-treated patients that reported possibly suicide-related AEs was higher (2.4%, 18/738) than the proportion reported by patients treated with placebo (1.1%, 7/647). The events in both treatment groups were predominantly in adolescent patients with depression. The number of cases reported was small and with such small numbers and with events that may have many complex contributing factors it is perhaps over-simplistic to assume that the numerically small difference in occurrence between the paroxetine and placebo group is attributable solely to drug treatment. It is possible that confounding factors may have contributed to this apparent difference. Indeed it would take only a small imbalance in confounding factors between treatment groups to remove the apparent difference between the groups.

Possible confounding factors have been assessed as far as possible in the paediatric patients for whom possibly suicide-related AEs have been reported. However, there can

be many factors that can contribute to a patient experiencing suicidal behaviour. Risk factors for suicide and attempted suicide among young people that have been identified in the literature include social and educational disadvantage, childhood and family adversity (which may include family violence, family arguments, not living with both parents, low level of parental support, frequent geographical moving, exposure to sexual abuse), psychopathology, and exposure to stressful life events and circumstances [Beautrais, 2003; Pelkonen, 2003]. Frequently, suicidal behaviours in young people appear to be a consequence of adverse life sequences in which multiple risk factors from these domains combine to increase risk of suicidal behaviour [Beautrais, 2000]. While we have been able to assess our paediatric clinical trial database for some risk factors, such as previous suicidal behaviour, presence of suicidal ideation at baseline and presence of comorbid anxiety, there are others for which we do not have the information to assess whether they may have been contributing factors in our study population or not. Such information is not collected in our clinical trial programmes. Without knowing such information on important risk factors for suicidal behaviour in children we cannot conclude that they were not contributing factors to the cases observed in our study. Hence, although unmeasured confounders should also have been balanced by randomisation, the possibility that confounding factors could have contributed to the excess of possibly suicide-related events seen in the paroxetine group cannot be excluded totally.

If we were to make the assumption that paroxetine treatment is indeed associated with increased occurrence of possibly suicide-related AEs or self-harm, any potential mechanism requires there to be a property of paroxetine to which adolescents and young adults are more susceptible than older adults or younger children. At present we are not aware of such a property although the possibility that a mechanism may be discovered in the future cannot be ruled out.

Returning to the theory of SSRI-induced akathisia leading to suicidal behaviour, it should be noted that 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 that had 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 the study [Appendix 3, Table 3.54]. 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 [Appendix 3, Table 3.51]. These data certainly do not support the theory that, in paediatric patients, paroxetine induces suicidal behaviour as a result of producing agitation or akathisia soon after starting treatment.

One other possibility to account for an excess of possibly suicide-related AEs in paroxetine treated adolescents is the possibility that paroxetine was converting patients with previously undiagnosed bipolar disorder into a first hypomanic or manic episode (and the risk of suicidal behaviour is higher in bipolar than unipolar disease [Jamison, 2000]). If paroxetine provokes the switch into mania or mixed manic/depressive states this could present most often in adolescents whose depressions mark the start of their bipolar disorder. In older depressed bipolar patients, their mania would have more likely declared itself in their 20's and hence older depressed bipolar patients are more likely to

have been excluded from our studies than younger ones. Pre-adolescents who would later develop bipolar disorder might be susceptible to this switching into manic/mixed states, but these states would not be likely to present with suicidal behaviour, which is exceedingly rare in this age group. However, review of the cases of the paediatric patients with possibly suicide-related AEs revealed that there was no greater improvement in depressive symptoms in such patients treated with paroxetine than with placebo (see Table 4.1, Table 4.2 and Table 4.3). None of the individual rating scale analyses shows a significant treatment benefit of paroxetine over placebo, and there is no evidence that efficacy improvement is greater among patients with a possibly suicide-related event. There is more evidence to support the opposite hypothesis. Hence, although it is possible that all patients switched by paroxetine could have been switched into "mixed" states of dysphoric mania in which improvement in depressive symptoms may not be apparent, these findings do not support a "bipolar" theory. Additionally, they do not support any other theories in which possibly suicide-related events are proposed to arise in some individuals as a consequence of improvement in the episode of depression. These include a "rollback phenomenon" [Fava, 1991], a theory in which, as the depressive illness remits, it returns in reverse order through many of the stages and symptoms that were seen during the time it developed. Thus a patient who had been suicidal sometime during a depressive episode and was not suicidal when pharmacological treatment was initiated may re-experience suicidal thoughts as the episode remits.

Table 4.1 Change from Baseline in HAMD Total Score by occurrence or non-occurrence of possibly suicide-related AE (Week 32 LOCF, Study 329)

	Paroxetine			Placebo		
Possibly suicide-related AE	**N**	**LS Mean**	**Std Error**	**N**	**LS Mean**	**Std Error**
Yes	8	-7.0	2.6	2	-7.4	5.2
No	82	-10.3	0.9	85	-9.3	0.8

Possibly suicide-related AE	**Treatment Difference**	**95% CI**	**P-value**
Yes	0.5	(-10.9, 11.9)	0.94
No	-1.1	(-3.3, 1.1)	0.34

Treatment Differences are paroxetine – placebo; negative differences correspond to treatment benefit. Model adjusted for baseline score and centre.

Table 4.2 Change from Baseline in MADRS Total Score by occurrence or non-occurrence of possibly suicide-related AE (Week 12 LOCF, Study 377)

	Paroxetine			Placebo		
Possibly suicide-related AE	**N**	**LS Mean**	**Std Error**	**N**	**LS Mean**	**Std Error**
Yes	9	-6.6	3.4	4	-5.8	5.0
No	172	-16.1	1.1	89	-14.8	1.2

Possibly suicide-related AE	**Treatment Difference**	**95% CI**	**P-value**
Yes	-0.8	(-12.8, 11.1)	0.89
No	-1.3	(-3.7, 1.2)	0.31

Treatment Differences are paroxetine – placebo; negative differences correspond to treatment benefit. Model adjusted for baseline score and centre.

Table 4.3 Change from Baseline in CDRS Total Score by Occurrence or Non-Occurrence of Possibly Suicide-Related AE (Week 8 LOCF, Study 701)

	Paroxetine			Placebo		
Possibly suicide-related AE	**N**	**LS Mean**	**Std Error**	**N**	**LS Mean**	**Std Error**
Yes	3	-24.5	8.8	1	-27.6	14.4
No	98	-23.4	1.8	99	-24.6	1.8

Possibly suicide-related AE	**Treatment Difference**	**95% CI**	**P-value**
Yes	3.1	(-29.5, 35.7)	0.85
No	1.1	(-3.0, 5.3)	0.59

Treatment Differences are paroxetine – placebo; negative differences correspond to treatment benefit. Model adjusted for baseline score and centre.
Patient 701.154.25768 had a possibly suicide-related AE but is excluded from this analysis because he had no post-baseline CDRS assessment

4.3. Conclusions

Experience from over 14,000 patients involved in paroxetine placebo-controlled clinical studies in adults do not support the suggestion that paroxetine may induce suicidal behaviour in adults. The proposal that paroxetine may induce suicidal behaviour as a consequence of inducing agitation or akathisia is also not supported by the evidence from the paroxetine studies.

More possibly suicide-related AEs have been reported in paediatric patients receiving paroxetine than placebo. However, as the number of events was small and confounding factors cannot be ruled out, it cannot be concluded from these data that paroxetine causes more of such events than placebo. Nevertheless, mechanisms by which paroxetine may induce suicidal behaviour in the paediatric population were considered and were not found to be supported by the data available.

4.4. References

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