SSRIs, aggression and suicide – a cause for concern or the result of media hype?

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In recent years, controversy has arisen in the lay press regarding the supposed increase in aggression and suicide in a small minority of patients taking SSRI antidepressants. It has been implied that such adverse effects are a possible result of drug-induced akathisia.[1,2] Counter arguments have been made that such rare changes in behaviour are a reflection of the underlying pathology of major depression in which agitation, aggression and suicidal ideation and attempts are frequent symptoms.[3]

It has been argued both in the media, and by some protagonists of the suicidal propensity of the SSRIs, that the pharmaceutical industry has knowingly suppressed the information regarding the potential danger of this group of drugs primarily for commercial reasons and that professional organisations and individuals who should be concerned about such dangers are duplicitous in ignoring the evidence.[4,5]

The media in Europe and North America in particular have focussed on a number of bizarre cases in which homicide, followed by suicide of the aggressor who has taken a SSRI (usually fluoxetine), has occurred.[3,1] Such dramatic cases have usually been followed by widely publicised court proceedings against the company who manufactured the drug and an out-of-court settlement of over a million dollars to the relative usually being the outcome of the case.[5]

In the less emotionally charged area of academic research, depressed patients who had been treated with an SSRI and complained of suicidal thoughts ceased to experience these thoughts when the drug was abruptly withdrawn; the suicidal thoughts returned when the SSRI was introduced.[6] This is the test-re-test scenario often used in clinical pharmacology to confirm a drug related adverse effect.

Aggressive and suicidal behaviour after SSRIs treatment

Beside such anecdotal reports, Teicher et al[7] reported in detail on the behaviour of six patients with depression, but not apparently suicidal, who developed intense violent suicidal thoughts following two to seven weeks of fluoxetine treatment. An interpretation of the findings of this study was complicated by the high doses of fluoxetine used (up to 80mg/day), by the multiple psychopathology of the patients and by the co-administration of other psychotropic drugs.

The authors however concluded that 4/6 patients complained of a sense of inner restlessness which may be interpreted as akathisia, a condition well known to occur in some patients, and estimated to be approximately 21%, on high doses of conventional neuroleptics[8-10] and other psychotropic drugs such as lithium,[11] benzodiazepines,[12] levodopa[13] and tricyclic antidepressants.[14]

The publication by Teicher et al[7] was followed by some other reports in the medical literature of aggressive, suicidal behaviour in some adolescent depressed patients following treatment with a SSRI.[15] More surprising was a recent report that somewhat similar symptoms occurred in several healthy volunteers who were participating in a clinical study of sertraline and fluoxetine.[5]

The suggestion that antidepressants, including the SSRIs, could initiate aggression and suicidal thoughts is contrary to the experimental and clinical evidence. For example, there are extensive studies in which the use of antidepressants have been shown to result in a reduction in the suicide rate in both men and women.[16]

Jick *et al*[17] estimated the rate and means of suicide among patients taking 10 different commonly prescribed antidepressants. Based on the very large data base of the General Practice Research Data Base of the UK, the authors concluded that the suicide risk was similar for all the antidepressants (these included six different tricyclic antidepressants, fluoxetine, mianserin, trazodone and flupenthixol). They also commented that while the suicide rate was slightly higher in those patients taking fluoxetine, this could be explained by a selection bias rather than by a hidden adverse effect of the drug.

There have been several meta-analyses of controlled trial in which the possible link between fluoxetine and suicide have been assessed. Those studies that report a lack of evidence for an association between fluoxetine and increased suicidal acts or thoughts come from both pharmaceutical company[3,18,19] and non-pharmaceutical company sponsored sources.[20,21]

Lack of association between SSRIs and suicide

MacKay *et al*[22] in their observational cohort study of four different SSRIs (fluoxetine, fluvoxamine, sertraline and paroxetine), found no difference between them in the number of successful or unsuccessful suicides. Neither did they differ in terms of these adverse effects in those patients being treated with tricyclic antidepressants.[23]

Quite contrary to the evidence that SSRIs increase suicide risk, there is evidence that both tricyclic antidepressants and fluoxetine actually reduce suicidal ideation and protect against the emergence of suicidal thoughts.[19] This is supported by the study of Kasper *et al*[24] who, in a study of the

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relationship between suicide and depression, concluded that antidepressants such as the SSRIs, due to their central serotonergic action, are of particular benefit to patients at risk from suicide.

Furthermore, Warshaw *et al*[20] in their study concluded that while there was no evidence that fluoxetine was associated with increased suicidal attempts, they did find that those depressed patients with more suicidal risk factors at the start of treatment would be more likely to be prescribed fluoxetine than those patients who did not have such risk factors.

This probably accounts for the selection bias reported by Jick *et al*.[17]

More recently Khan and Brown[32] in their analysis of 48,277 depressed patients participating in randomised controlled trials against placebo, found that 77 patients committed suicide. Based on patient exposure years, similar suicide rates were seen among those randomly assigned to a SSRI antidepressant (0.59%), a standard antidepressant(0.76%) or placebo (0.45%).The authors conclude that there is no evidence that there is an overall difference in the suicide risk between antidepressants and placebo treated depressed patients in controlled trials or a difference between SSRI's, other antidepressants or placebo. In another recent study, Hall *et al*[33] examined the association between trends in antidepressant prescribing and suicide rates in Australia for the period 1991 to 2000. They found that although the overall national suicide rates did not fall significantly over this period,the incidence decreased in older men and women but increased in younger adults.Of particular importance was the finding that the higher the exposure to antidepressants, the greater the decline in the rate of suicide. This association was most apparent in the older age group of depressed patients.These findings concur with those of Carlsten and colleagues[34] in Sweden who found that the suicide rates declined over the period 1977-1997 and that the rate of decline accelerated after the SSRI's were introduced in 1990. Rihmer[35] also reported a decline in the suicide rate in Hungary following the introduction of the SSRI's in the early 1990's despite the steep increases in unemployment and in alcohol consumption. Thus the evidence from objective studies on the possible association between the use of SSRI's in depressed patients and increased suicide risk is negative. Indeed, it would appear that the increased presribing of SSRI's produces a quantifiable benefit to mental health.

It is not without interest that the Department of Health in the UK[25] has stated that the available evidence does not support an increased risk of suicide following SSRIs but warned that: "Prescribers and patients should be aware that it is general clinical experience that the risk of suicide may increase in the early stages of treatment with any antidepressant". In the US, the Food and Drug Administration[26] has stated more directly that: "There is no credible evidence of a causal link between the use of antidepressants, including fluoxetine, and suicidality or violent behaviour".

The question now arises whether the anecdotal reports of suicide, homicide and violent behaviour in depressed patients being treated with SSRIs are caused by the drug or the illness. As Walsh and Dinan[27] noted in their review, a high proportion of patients prescribed the SSRIs have made previous suicidal attempts which is why they have been given antidepressants which, unlike the older drugs, are both effective and safe.

Furthermore, many of the anecdotal reports of emergent violent or suicidal acts in which fluoxetine was administered were reported to occur before the antidepressant effect of the drug became apparent. It therefore makes it difficult to argue that a SSRI, or indeed any antidepressant, is the actual cause of the increased suicidal or violent behaviour.

In regard to the increase in irritability and aggression that has been observed in the anecdotal reports from depressed patients on SSRIs, there are several large studies of patients with Alzheimer's disease or vascular dementia in which citalopram or sertraline have been shown to attenuate the symptoms of irritability, restlessness and aggressiveness.[28-30]

Whether akathisia is an idiosyncratic factor that initiates the violent or suicidal attempts in those rare cases in which these behaviours have occurred is unknown.

Conclusion

In conclusion, the absence of objective data implicating a causal relationship between violence, suicide and the use of SSRIs in depression strongly contradicts the reports that have been highlighted by the media. Such reports can only serve to increase the concerns of the depressed patients and their families regarding antidepressant medication, the outcome of which could be an increase in non-compliance leading inevitably to a risk of increased suicide.

Declaration of Interest: None

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