CNS Drugs 2 (3): 252-254, 1994
1172-7047/94/0009-0252/$01.50/0

The Fluoxetine and Suicide Controversy
A Review of the Evidence

The recent review article on the postulated association between fluoxetine and the emergence of suicidal behaviour by Dr Healy[1] may be misleading to clinicians.

The evidence that he suggests is 'emerging' relating to fluoxetine and suicidal ideation consists of a small number of case reports.[2] There are no scientific data to support a causal link between fluoxetine and suicidal ideation. Indeed, a meta-analysis of double-blind clinical trials involving over 3000 patients that compared fluoxetine with placebo and tricyclic antidepressants demonstrated fluoxetine may even lower suicidal ideation.[3] Other meta-analyses of patients treated for obsessive-compulsive disorder[4], obesity[5] and bulimia nervosa[6] also fail to demonstrate any link between fluoxetine and suicidal acts or ideation. We agree with Dr Healy that 'these data from several thousand patients and the evidence that fluoxetine reduces suicidal ideation, must on any scientific scale outweigh the dubious evidence of a handful of case reports'.[1]

Why then does he appear to give credence to anecdotal reports? The theory that akathisia underlies a putative increase in suicidal ideation is unsustainable for 3 reasons. First, akathisia is seen with distressing frequency in patients treated with antipsychotics, yet any association between this symptom and suicidality in such patients is not proven. Secondly, there is no evidence to suggest that fluoxetine is associated with akathisia any more than other antidepressants. The Drug Safety Research Unit (DSRU) in Southampton, UK monitored 12 692 patients who had been treated with fluoxetine.[7] The term 'akathisia' does not appear in these data as an adverse event, and even if it is assumed to be covered by 'agitation' and 'anxiety' the incidence is 12 per 1000 patients. This is comparable with 20.4 per 1000 for fluvoxamine and 10 per 1000 for paroxetine. Thirdly, a further analysis of the fluoxetine clinical trial data has failed to confirm the hypothesis that some patients treated with an antidepressant who develop akathisia experience treatment emergent suicidality.[8] In 3065 patients there was, in fact, no evidence to suggest a relationship between akathisia and suicidality. The incidence of activating events (agitation, akathisia, anxiety, CNS stimulation, insomnia and nervousness) in this population was 1.1% – comparable with the DSRU findings.

Dr Healy criticises the use of item 3 of the Hamilton Depression Rating Scale (HDRS) for assessing suicidality of patients enrolled in clinical trials, but without supporting evidence. His statement that 'investigators will tend to mark down any scores on this item in line with a general marking down of HDRS scores as a patient in a trial improves' is not supported by the literature. Indeed, many of the currently used suicide rating scales have been standardised on the HDRS item 3.[9-11] Should the intense suicidal urge as described by Teicher[2] be present, it is of such severity that it is very unlikely to be either missed by an investigator or not reported by a patient.

In trying to strengthen the putative link between serotonin (5-hydroxytryptamine; 5-HT) and suicide, Dr Healy describes 4 case reports by Damluji and Ferguson,[12] in which suicidal ideation occurred apparently in association with desipramine treatment. Desipramine, however, has little effect on central serotonin levels as it acts primarily on noradrenergic neurotransmission.[13] In addition, 2 of these patients subsequently responded to fluoxetine, as an alternative to desipramine, and did not experience a return of suicidal ideation.

Dr Healy also considers the study by Rouillon et al.[14] as support for his hypothesis. However, this complex study was not controlled either for compliance or for equal distribution of patients between the treatment arms. Most of the patients received subtherapeutic doses of maprotiline, and the number of cases associated with suicidal behaviour was too small to justify major conclusions.

Dr Healy's review does not put into perspective the very few case reports of suicidality in comparison with the rigorous meta-analyses that have failed to find any such association. The Food and Drug Administration (US) and Medicines Control Agency (UK)[14] have both stated that they could not find any association between antidepressant pharmacotherapy and the emergence and intensification of suicidal ideation, yet Dr Healy assumes that virtually all antidepressants have this potential.

The most important clinical message about depression and suicide is that suicidal thoughts and acts are part of the depressive syndrome. These phenomena can worsen during the course of a depressive illness – a fact highlighted by the finding that suicidality is more likely to worsen among placebo- than active medication-treated patients in controlled clinical trials.[3] Clinicians involved in treating depressed people have to be constantly vigilant for signs of suicidal thoughts, as prompt intervention can save the patient from suicide. It is quite unjustified to attribute this emergent finding to the medication that has been taken during the illness.

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The author's reply:

Dr Nakielny and myself agree that the risks posed by untreated depression far outweigh the risks that arise from treatment. We should not, however, focus exclusively on the former to the neglect of the latter set of risks.

Dr Nakielny refers to a hypothesis, which it appears she assumes I have, that links serotonin to suicide. Far from having such a hypothesis, my efforts to review the literature[1] in this regard were designed to convey a message that any attempts at a hypothesis that would link neurobiology to suicidal behaviour are premature.

If I have a hypothesis (and it should be remembered that this was a review article), it is as follows. The detection and management of the emergence of suicidal ideation in patients treated with any psychotropic medication is a matter of medical sensitivity. Furthermore, an increase in sensitivity is needed where the prescription of all antidepressants and both antidepressants and antipsychotics are required. There does not appear to be anything inherently different about fluoxetine in relation to other antidepressants in this regard. I still use it regularly in clinical practice. Why then 'pick on' fluoxetine? Simply because the issue has come to prominence, for whatever reason.

My comments about the relative merits of clinical trial data and properly conducted case reports

involving tests and retest designs were intended to be somewhat ironical. The data from a single properly observed and reported case study can be as valid as that from several thousand patients subjected to clinical trial procedures. The fact that the 2 data sets on the surface would appear to be at odds with each other should stimulate investigators, rather than lead them to dismiss one data set out of hand. In the instance of the case report literature, there is a consistency across reports, and in some cases, a proper test-retest design has been employed. These reports are also consistent with clinical wisdom, i.e. patients who are depressed often commit suicide after a week or two of treatment and that patients taking antipsychotics often attempt to kill themselves shortly after treatment has been instituted or changed. The fact that a relationship between akathisia and suicide has not been 'proven' does not mean that such a relationship cannot be postulated or even assumed. The relationship may need to be investigated further. Clearly, given the current circumstances, those involved in researching and prescribing should not be precluded from responsible discussion about the possibility of such as relationship.

As regards the reliability of item 3 on the HDRS, other instruments designed to rate suicidal ideation and behaviour may well have been standardised against item 3 of the scale. In the course of such standardisation studies, this item may have performed reliably. However, this does not mean that it will perform in a similarly reliable manner when used in clinical trial situations, in which the bias of a halo effect (a well established phenomenon) can be assumed to occur.

The above issues need to be debated fully and, accordingly, I welcome Dr Nakielny's letter. I would also stress, as she does at the end of her letter, that such debates need to take place against a background of recognition that depression remains far too often unrecognised and untreated, and that untreated depression is much more likely to lead to suicidal ideation and behaviour than is the treatment.

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