hypomanic symptoms of depressive mixed states. At least 50% of outpatient depressions in clinical practice are bipolar II [10, 13, 21, 23], supporting the need to assess carefully hypomanic symptoms during a depression (which cannot be done by following strictly the Structured Clinical Interview for DSM-IV). The possible worsening of depression by SSRIs, including suicide induction, seems more related to psychiatric clinical skills than to the type of antidepressant. Prospective, controlled studies comparing suicide risk during antidepressant treatment in depressive mixed state (unipolar and bipolar II) and in non-mixed depression could be useful to clarify the relationship between antidepressants and suicide observed in some patients. In conclusion, what this article does clearly show is that not treating depression with SSRIs is much more risky (more suicides) than treating depression with SSRIs. What this article importantly highlights is that antidepressants can worsen depression, which however may be more related to the clinical features of depression than to a class of antidepressants. Use of mood stabilizers during antidepressant treatment of depression could be a safeguard against the worsening of depressive mixed states.

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Reply

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Drs. Rihmer and Benazzi have made useful contributions to the general debate on suicide and treatment and the adverse effects of antidepressants in the past and have made further useful contributions in their letters. Hopefully these responses to the points they raise will add to this debate.

Dr. Rihmer notes that the suicide rate on placebo in SSRI trials was higher than the suicide rate on placebo in non-SSRI trials. He fails to take into account that the previously published suicide and suicidal act rate on placebo in paroxetine trials was even higher than the suicidal act rate that I have recorded here. Essentially, the data submitted to the Food and Drug Administration (FDA) for suicidal acts on placebo in 1989 contained 1 case in 554 patients, in contrast to the figure of 3 recorded in my analysis. Following the emergence of a fluoxetine controversy in 1990, the FDA files and the subsequently published data on suicidal acts on placebo in these paroxetine trials increased to 2 suicides and 6 suicidal acts from 554 patients [1]. It is clear that something similar has happened in the fluoxetine and sertraline trials.

I have no further information as to the validity of the placebo figures for either citalopram or venlafaxine, but against this background, it is difficult to have confidence in these figures and it is more likely that the figures for suicidal acts on placebo in SSRI trials in general are lower than noted in my article and not higher than the figures for suicidal acts on placebo in non-SSRI trials.

A recently published re-analysis of FDA databases by Khan et al. [2] fails to take this point into account. In their study, rates of suicide are recorded as follows: in 26,109 patients on SSRIs, there were 38 suicides, while in 17,273 patients exposed to other antidepressants, there were 34 suicides and in 4,895 patients exposed to placebo, there were 5 suicides. Whether the data were calculated in terms of absolute numbers or patient-exposure years, the figures for suicide on placebo were lower than for SSRI or other active agents. This in its own right undercuts claims that SSRI use can be expected to lower suicide rates. But an equally important fact is that of the 5 suicides these authors cite as occurring on placebo, at the most 2 did so and there can be no certainty that even these 2 did so. Analyzing the figures taking this into account points to a significant problem with treatment.

As regards the further points made by both Drs. Rihmer and Benazzi, it is not my position that SSRIs will always trigger suicidality. Along with Dr. Benazzi, I believe these drugs can have positive effects on both suicidal and aggressive states. My position is that given the conclusive evidence from case-control studies that SSRIs can trigger suicidality in some, our efforts to reduce suicidality in general would be better assisted if these drugs came with appropriate warnings. RCT and epidemiological data do not prove cause and effect but can indicate whether a problem is happening with sufficient frequency to warrant warnings, and the data from these sources seem to me to indicate that antidepressants are even more likely to be associated with a lowering of suicide rates if their use is accompanied by the proper warnings and clinical monitoring.

Dr. Benazzi might like to note that in the course of the development programme for sertraline at a time when this drug had approximately 8,000–9,000 patients entered into clinical trials, there had been 252 suicidal events recorded. In the case of 25 of these, the investigator had made a causal determination that these events were linked to the drug. In the case of a further 29, where the investigator had not thought these events were linked to the drug, Pfizer monitors determined that their drug was associated with the suicidal events in question [3].

Both the clinical investigators in the first instance and Pfizer in the second instance made these causal determinations by applying the standard rules for cause and effect determination, which involve challenge, de-challenge, and re-challenge, as well as indications from dose response curves and indications from the effects of antidotes on the target adverse effect. It seems that such procedures work very well in the case of sleep disturbances caused by SSRIs, which may also be a feature of depression, sexual dysfunction caused by SSRIs, which may also be a feature of depression, anorexia caused by SSRIs, which may also be a feature of depression; however, for some strange reason, we are not prepared to consider that suicidality can be caused by drugs as well as by the illness.

Unlike clinicians, the various pharmaceutical companies have also experience from studies in healthy volunteers, where agitation has been provoked in a dose-dependent manner by SSRIs, and there have been frequent drop-outs for serious disturbances of previously normal mental states. Part of the problem readers of this journal face is that the bulk of this material, along with the raw data for suicides occurring on placebo in clinical trials, remains unpublished. I am sure that most of us could unite on a proposal that patient safety would be best served by a full disclosure of all relevant raw data.

As regards national suicide rates, these are notoriously difficult to interpret. For example, in the United Kingdom, there has been a recent fall in suicide rates that probably bears little relationship to any detection or treatment of depression. Approximately 8 years ago, coroners were encouraged to return open verdicts if they were not entirely satisfied that the person committing the act intended to do so. 'Suicide' while under intoxication with LSD for example would not lead to a verdict of suicide. Classic SSRI-induced cases of 'suicide' therefore can and have in fact attracted an open verdict at inquest in the United Kingdom.

Furthermore, aside from directions to coroners to be more conservative in returning suicide verdicts, the National Health Service has set up a reduction of suicide as an outcome measure that the health service should strive for. Against this background, it would seem almost impossible to determine what contribution 'data management' of this issue might make as against the recognition or treatment of depression. In the case of Ireland, there is a statistically significant association between SSRI intake and suicide compared with non-SSRI intake and suicide that would not be expected to hold if the religious issues Dr. Rihmer notes were as critical as he suggests they might be.

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