

and several Western European countries in the last few decades have been accompanied by the markedly increasing use of ADs, mainly SSRIs. Dr. Healy mentions the case of Italy and Ireland, where the slight rise in national suicide rates were accompanied by an increase in SSRI use. These 2 countries might be among the few exceptions to the general European trend mentioned above. Both Italy and Ireland are traditionally catholic countries with relatively low suicide rates, and the recent positive change of attitude of the Catholic Church regarding suicide can result in its more reliable registration, leading to a virtual increase in suicide rates.

The everyday clinical practice clearly shows that successful treatment of major mood disorders substantially reduces suicide morbidity and mortality in individual cases, and there are several long-term clinical studies showing the same on large samples of mood disorder patients [5, 7]; therefore, it is logical to assume that if the rate of effectively treated depressions in the population increases gradually, it will at a given point appear in the decline of the suicide rate. However, since the effect of a given (and effective) intervention largely depends on the baseline situation, i.e. the effect is greater when the baseline situation is more pathological, the role of better treatment of mood disorders in reducing suicide rates can be easier to demonstrate in populations where the suicide rate is high and the rate of treated depressions is low. On the other hand, in countries where suicide is rare and the rate of treated depressions is relatively high, no significant effect would be expected, at least in short term.

Since only a small minority of depressed suicide victims have received adequate AD pharmacotherapy at the time of their deaths [3, 5, 7], more widespread treatment of depression remains among the main methods of suicide prevention [3, 7]. Regardless of this, however, the possibility that certain classes of ADs can rarely induce suicide behaviour in vulnerable persons might be a real problem and, as also mentioned by Dr. Healy, requires further studies.

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Dr. Zoltán Rihmer, MD, PhD

In- and Outpatient Department of Psychiatry No. XIII  
National Institute for Psychiatry and Neurology  
HU–1281 Budapest 27, Pf. 1 (Hungary)  
Tel./Fax +36 1 3558 778, E-Mail rihmer.zoltan@posta.net

*Psychother Psychosom* 2003;72:358–359

DOI: 10.1159/000073034

#### Do SSRIs Cause Suicide?

Franco Benazzi

Collaborating Center, University of California at San Diego, Calif., USA; Outpatient Psychiatry Private Center, Ravenna and Forlì, Department of Psychiatry, National Health Service, Forlì, and Department of Psychology, University of Bologna, Bologna, Italy

I read the important paper by Healy [1] on the possible causal link between suicide and selective serotonin reuptake inhibitors (SSRIs). The conclusion is that 'the data reviewed here, which indicate a *possible* doubling of the relative risk of both suicide and suicide attempts on SSRIs compared with older antidepressants or *no treatment*, make it difficult to sustain a null hypothesis'. I believe that spreading ideas about 'possible' associations between antidepressants and suicide should be done carefully and only when supported by strong findings, as estimates of suicide risk in depression range between 6 and 18.9% [2–4]. Combining data from different studies (different methods, different samples) is not correct statistically.

In the present study, there is a mixture of findings from different studies: controlled case studies, efficacy studies, meta-analyses of studies, epidemiological studies, healthy volunteer studies. In table 1 [1] the number of reported suicides is between 0 and 9, and the sum leads to the figure of 16 suicides during SSRIs treatment of 10,611 patients, a risk of 0.0015 (i.e., 1.5 suicides for every 10,000 treated patients). In table 2 [1] SSRIs have 110 suicides during treatment of 50,150 patients, a risk of 0.0021 (i.e., 2.1 suicides for every 10,000 treated patients). These data come from primary care where psychiatric clinical skills are not the best. In table 3 [1], again based on primary care, fluoxetine has 11 suicides during treatment of 11,860 patients, a risk of 0.0009 (i.e., 9 suicides for every 10,000 treated patients). The comparison between the reported risk of suicide in SSRI-treated depression (1–9 for every 10,000 patients) and the risk of suicide in untreated depression (6–18.9 for every 100 patients) [2–4] is striking. It was found that treated versus untreated unipolar and bipolar depressions had a very different risk of suicide (18.1 versus 5.2%) during a long follow-up [3]. A 'dose-response' relationship to support a causal link between SSRIs and suicide is suggested by Healy, based on a possible relationship between induction of agitation by SSRIs and suicide. The controlled studies by Fava et al. [5–7] have shown that anger and agitation in unipolar depression can *improve* with fluoxetine. Fluoxetine was also shown not to induce suicide [8, 9]. However, antidepressant treatment of depression presenting concurrent manic/hypomanic symptoms (which may be undetected if depression is not assessed carefully) [10–19] may lead to the increased severity of these symptoms, which could lead to suicide [18, 20, 21]. Underdiagnosis of bipolar (type-I, and much more type-2) depression is high in clinical practice [22]. Systematic, skilful probing for past manic/hypomanic episodes and for concurrent manic/hypomanic symptoms during assessment of depression can detect a large number of misdiagnosed bipolar (mainly bipolar-II) depressions. These depressions with concurrent manic/hypomanic symptoms (depressive mixed states) are common in bipolar II (50%) (and also in unipolar, 20%) outpatients [10–19]. Antidepressants used without mood stabilizers can have negative effects on the manic/

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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Dr. Franco Benazzi, Via Pozzetto 17  
IT-48010 Castiglione di Cervia (Italy)  
Tel. +39 335 6191 852, Fax +39 054 330 069  
E-Mail f.benazzi@fo.nettuno.it

*Psychother Psychosom* 2003;72:359–360  
DOI: 10.1159/000073035

### Reply

David Healy

North Wales Department of Psychological Medicine,  
Hergest Unit, Ysbyty Gwynedd, Bangor Gwynedd, UK

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.