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Do SSRIs Increase the Risk of Suicide among Depressives Even if They Are Taking Only Placebo?

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I have read with great interest the paper by Dr. Healy [1], reviewing an unselected cohort of randomised clinical trials (RCTs) and demonstrating a possible doubling of the relative risk of committed and attempted suicides on SSRIs, compared with older antidepressants (ADs) or placebo 'treatment'. Analysing the data of table 1 of his paper, it can be seen that the rate of suicide behaviour (suicides and attempted suicides combined) among the SSRI trial placebo patients is 0.66% (16/2,401), whereas the same figure among the non-SSRI trial placebo patients is 0.23% (4/1,739). Does this mean that, compared with other ADs, SSRIs increase the risk of suicide behaviour almost threefold even if the patients are taking only placebo? Obviously, it does not.

The result of this simple calculation, unfortunately missing from the table of Dr. Healy, is enough to question basically the main conclusions of his paper; yet this is not the point I should like to make here, for, in spite of this shortcoming, the paper merits further attention. The correct clinical interpretation of the findings presented by Dr. Healy calls for a more detailed analysis, taking into account the time of suicide behaviour and the responder/non-responder status of the patients at the time of their suicide event during the trial as well as the time and source of drop-outs among patients taking ADs or placebo. In other words, it would be important to secrete the data of the RCTs on: (1) suicide events occurring in the first 3 weeks of the trials (i.e. before the onset of the action of ADs), (2) suicide events occurring after the 3rd week of the trials among non-responders, (3) suicide events occurring after the 3rd week of the trials among responders, and (4) the time and source of drop-outs among patients taking placebo or ADs.

Theoretically, the higher rate of suicide events after the 3rd week of treatment in patients on SSRIs compared with older ADs might be related to the higher rate of SSRI non-responders. If it were the case, the conclusion that SSRIs induce suicidality more often than older ADs is incorrect, and the formulation 'among non-responders, SSRIs prevent less suicidal behaviour than older ADs' would be more precise. It has been demonstrated, e.g. that lithium has an independent anti-suicidal effect, since the risk of suicide behaviour decreases significantly not only among prophylactic lithium responders, but also among partial responders and non-responders as well [2]. On the other hand, if the rate of drop-out because of suicidality among depressed patients taking placebo in RCTs were much higher than

that of the patients taking ADs, it could be explained why suicide behaviour among depressed patients is the lowest on placebo.

Since randomisation results in the same severity (including suicidality) of patients on placebo and on active treatment arms, the exact answers to the above-raised questions could resolve the contradiction between the logically correct conclusion and the clinically unacceptable interpretation of the findings presented by Dr. Healy, i.e. placebo treatment results in the lowest risk of suicide in depressed patients. As for suicide events occurring in the first few weeks of the trials, it should be noted that the well-known sedative (side-) effect of older ADs (clomipramine and others) that cause several problems during long-term pharmacotherapy can decrease/prevent accompanying/newly emerging anxiety (or akathisia) in the early stage of the treatment; however, this is not the case for the SSRIs. On the other hand, because of the more favourable side-effect profile of SSRIs than that of older ADs, it is relatively easy to keep depressed patients on these drugs for many weeks or months, even if they are non-responders. If an 8-week randomised, double-blind, placebo-controlled, fixed dosed antidepressant study were performed in the line of good clinical *real* practice (rather than in the line of good clinical *trial* practice), all non-responders would be dropped out between the 4th and the 6th week, and the final sample should contain only the responders (or, more precisely, the responders plus only a few percent of patients who were responders at the 6th week, but relapsed afterwards).

I will, of course, not reject the possibility that SSRIs can induce suicidality in a quite small subsample of depressed patients, whereas they reduce/vanish it in the majority of the cases. Whether SSRIs provoke suicide behaviour in the first 3 weeks of the treatment, or after the 3rd week, but only among non-responders, is mainly a technical problem to be resolved by giving concomitant anxiolytics in the first few weeks for all depressed patients and switching to SSRI after the 3rd week in non-responders. Of the remaining 2 possibilities, namely that SSRIs can induce suicidality at any time of the treatment regardless of clinical response and that SSRIs can induce suicidality but only after the 3rd week and mainly among responders, the latter, I think, is the most unlikely.

It should also be noted that the majority of RCTs on pharmacotherapy of depression exclude the most suicidal patients; therefore, their results are not representative of all depressives and have only a limited value regarding suicide prevention.

Dr. Healy also concludes that the increasing use of ADs (primarily SSRIs) cannot lower national suicide rates, which seems to be rather premature. He only mentions the findings of Isacson [3] on the significant inverse relationship between the use of ADs and suicide rate in Sweden, but does not consider the same significant negative correlation also reported for Denmark, Finland and Norway in the very same paper [3]. In addition, the more than 30% decrease in the very high suicide rate of Hungary in the last 15 years [4, 5] and the 20% decline in the suicide rate of England and Wales between 1960 and 1997 [6] as well as a marked drop of the suicide rates of Austria

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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Do SSRIs Cause Suicide?

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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/