Selective Serotonin Reuptake Inhibitors and Suicide: Is the Evidence, as with Beauty, in the Eye of the Beholder?

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Introduction

The recent debate started by David Healy [1] on the pages of this journal and further fueled by letters published in this issue [2–4] sparks again the decade-old debate ‘as to whether selective serotonin reuptake inhibitors (SSRIs) can trigger suicidality in vulnerable individuals’ [1]. The article by Healy [1] is carefully and elegantly written, and avoids definite statements, however the effect is, like in any good propaganda, that the reader may conclude that SSRIs at least increase the risk of suicide, if they do not outright cause it. The question for a careful and analyzing reader remains: Is that so? Is the evidence there?

Giovanni Fava [5] on the pages of this journal quotes Chomsky’s [6] work on propaganda and its mechanisms – namely filtering information (selective perception), engineering opinion, using the public relations industry and marginalizing dissident cultures. Sifting through Healy’s [1] article and the literature on SSRIs and suicide, I started to wonder how many of the described mechanisms of propaganda or at least some of its elements mentioned by Fava [5] are part of this debate. Many perceive propaganda as something coming to us from big government, ‘big brother’, special interest groups or big corporations. However, propaganda does not have a single set of parents, or a specific address. There is no doubt that the field of medicine has been flooded by propaganda from the pharmaceutical industry. The pharmaceutical industry

has certainly been filtering the information coming to us, engineering opinions, using public relations industry and marginalizing the few remaining dissidents. We have become oblivious, numb and superficial in critically evaluating and incorporating scientific information – how many of us go beyond reading the abstract of most, if not all, scientific articles? During the few and short lucid moments of attempting to reconcile our greed with our conscience, we may feel guilty and cheering the dissidents. We may feel especially strong in our cheering if these ‘dissidents’ are such skillful writers as David Healy. I have to admit that I loved his statement that, ‘The psychobabble of yesteryear is being rapidly replaced by a new biobabble’ [7]. How succinct and how true!

Nevertheless, while reading the article on SSRIs and suicide [1], I begin to wonder whether propaganda in this, like in many previous cases, could also originate on the other side of the debate, i.e. among the ‘dissidents’. It is important to realize the amount and pressure of propaganda in any debate and especially in a ‘scientific’ one, on both sides of the ‘aisle’. As the readers of the journal are mostly familiar with Healy’s [1] article and the ensuing correspondence [2–4], I decided to ‘analyze’ a bit his article and letter with respect to their arguments, interpretation of data and writing style regarding the possible stylization of scientific argument into propaganda. I will also discuss a few new articles that appeared in press during this debate. On purpose, I tried to avoid analyzing and discussing the entire literature on SSRIs and suicide. That

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would probably require a separate issue of the journal and would present an endless judgmental debate about which articles provide better evidence.

I hope that my discourse may provide the reader of a debate with some guidance on how to resolve the difficult and controversial issue – SSRIs and suicide – in his/her mind. However, I would like to forewarn those who are looking for a definitive answer, as I am not sure there is one. There is not any, and neither Healy's nor my articles provide one.

Let's delve into the argument and the article(s) in question.

Article by Healy [1]

Controlled Case Studies

Healy [1] notes that several studies cited in this part of his article are '... from authors noted for their expertise on akathisia'. I do not want to discard the expertise of my venerable colleagues mentioned here (R.A. King, P. Masand, A. Rothschild, W. Creaney, D. Healy, W.C. Wirshing, T. Van Putten and others) – most of them are well-known experts in psychopharmacology. However, they have written very little if anything on akathisia, besides reports on SSRIs, suicidality and a possible role of akathisia. The reader may consider this to be a minuscule point, but I feel that the case of 'akathisia' experts is a good example of what can be done with good use of language. Is this a subtle part of opinion engineering mentioned as one of the mechanisms of propaganda? I leave it to the reader. The next reference is to the article by Lane [8]. Healy [1], referring to this article, states that, 'a subsequent series of reports of suicidality and akathisia on sertraline and paroxetine pointed to the possibility of an SSRI-induced suicidality being a class effect.' While this comprehensive review article discusses the issue of SSRI-induced akathisia and suicidality, it does not discuss SSRI-induced suicidality being a class effect. The conclusion one can draw from reading the review of case-controlled and not controlled studies is that suicide may occasionally happen among patients treated with SSRIs as it happens in patients treated with other antidepressants. However, the opinion-engineering leaves one in doubt about the 'lines of evidence'.

Efficacy Studies

This section reviews articles analyzing data from the Food and Drug Administration (FDA) database. Studies in the FDA database, as pointed out by Healy [1], were

not designed to assess whether SSRIs could trigger suicidality. Most of the articles cited here [9–12] focused on the issue of whether there is an increased risk of suicide among placebo-administered patients in clinical trials from the FDA database. There was none. As Healy [1] pointed out, the absolute number of suicides was higher among patients treated with antidepressants (either investigational drugs, which were not only SSRIs, or active comparators). However, the authors in all those studies did not find any statistically significant difference between the investigational drug(s), active comparator and placebo in the frequency of suicide or suicidality.

While the data from the FDA database is interesting and intriguing, I found it hard to make a solid conclusion about suicide rates based on this data. The disparity between the number of patients on investigational drugs and the number of patients on placebo is intriguing. An example is the summary table by Healy [1]: 18,474 patients on all investigational drugs, 4,140 on placebo, 10,611 on SSRIs, and 2,401 on placebo in SSRI trials. How balanced are these studies? Shouldn't these studies be evened out? Shouldn't the data be balanced in regards to time of exposure? (Healy argues it should not, but one might argue that within the placebo-controlled studies it should.) How did these studies get to such a disparity in numbers? How many patients discontinued early in each group and thus their suicide risk could not be fully appreciated? Should data on anxiety patients be analyzed separately from those on depressed patients? Should the data be combined in a meta-analysis such as the one provided by Healy [1] when Khan [12] suggests that combining these data into a formal meta-analysis is not possible? It is also known that the early FDA database data on SSRIs (prior to 1992) does not provide the most reliable data on suicide. There was dissociation between the efficacy and safety data in those early studies. More attention has been paid to suicide and suicidality only since 1992 [A. Khan, personal commun.]. Or could it be that even the use of patient exposure-years may be seriously misleading as suggested by Kraemer [13]. Kraemer [13] also states that a better procedure would be to compare the survival curves with suicide or suicide attempts for the subjects in each study. She felt that if the constant hazard model did not hold here, in these studies, the suicide rates reported by Khan [9] were meaningless and the statistical tests invalid.

To complicate the issue of using data from the efficacy (and other) trials: Is it also possible, as Hirschfeld [14] suggests, that 'some depressed patients may have been too apathetic and fatigued to commit suicide during the depths of their depression, but may have experienced an

early treatment-related increase in energy that preceded any substantial improvement in mood and thinking, thereby increasing the risk of suicide?"

Finally, is it possible that the difference in SSRI and placebo suicide rates could be, at least partially, due to the different ways the placebo and SSRI data in the FDA studies were accumulated, as suggested by Leber [15]? He explains that the placebo patient-time was derived almost entirely from phase 2 and 3 trials, and therefore represents experience accumulated during a brief interval (e.g., 1–8 weeks) of fairly intense and repeated clinical observation and supervision. He explains that, 'although some portion of active treatment patient-time was gathered under identical conditions, the bulk was probably accumulated in open extension studies wherein patient surveillance and supervision are typically far less frequent and intense than they are in randomized trials'.

Meta-Analyses of Suicidality on SSRIs

Here Healy [1] argues several valid methodological problems with meta-analyses. While one would certainly agree with them, these points could be used in an exactly opposite argument. The first point states that Lilly's studies were not designed to test whether fluoxetine could be associated with the emergence of suicidality. True. But how could most of the data used in Healy's [1] argument be used to support the association of suicidality with SSRI administration? The studies Healy [1] uses for his argument were not designed to test this hypothesis either. The second point emphasizes that some of the Lilly studies had been rejected by the FDA. We do not know anything else about these studies. Would every study used by Healy [1] in his arguments meet the FDA standard? I doubt it. The third point states that only 3,067 patients of the approximately 26,000 were included in the meta-analysis. Again, the point would be not only how many patients were excluded, but why. Were they all appropriate for the meta-analysis? I don't know, but a clarification would certainly help. The next point refers to the co-prescribing of benzodiazepines to minimize agitation. Again, a valid point, but using the logic of this article, Healy [1] mentions earlier that benzodiazepines could trigger suicide, too.

As I stated earlier, these are all valid points that could be used on both sides of this debate. Again, it depends on the eye of the beholder.

Studies in Recurrent Brief Depression

I mention this part only to be complete – none of the studies in this part really contributes significantly to any of the sides of this debate.

Epidemiological Studies

Healy [1] states here that a series of what have been termed epidemiological studies has been held to exonerate SSRIs, and he goes on to discard one report after another. His tone and writing style already suggest the conclusion. Let us start with the first one: Healy [1] states that it is a one-column letter involving no suicide. True, this letter involves no suicide. However, the letter [16] discusses suicidal ideation in response to the original Teicher et al. [17] letter used by Healy [1] at the beginning of his discussion. It just does not confirm the observation made by Teicher et al. [17]. The second reference [18] is far from being an epidemiological study, it is a retrospective chart review as Healy [1] states and is far from being conclusive even after reanalyzing the data [19] and again should not be counted as an epidemiological study. The next two studies cited [20, 21], included 'only 192' and 'only 182', and 'none ... were clearly designed to establish whether fluoxetine might induce suicidality'. The same argument again, which goes for both sides of the discussion.

Let's turn to studies that, according to Healy [1], have not exonerated SSRIs. Healy [1] starts with two postmarketing surveillance studies [22, 23], which, as he points out, were not truly epidemiological either. However, here Healy [1] does not emphasize that these studies were not clearly designed to establish the association between SSRIs and suicide either. A further look at these studies is even more interesting. Healy [1] states that these studies, 'comparing SSRI with non-SSRI antidepressants, found an increased rate of induction of suicidal ideation, although not suicide attempts, or suicides with SSRIs'. Possibly true in the case of the first study [22], which compared fluoxetine and trazodone (not an SSRI, but a drug with some effect on serotonin reuptake, too). The incidence estimates of suicidal ideation (trazodone: 0.25%, fluoxetine 0.76%) were nonsignificantly different ($p = 0.0784$). Not true in the case of the second study [23]. This study [23] compared actually two SSRIs, fluoxetine and sertraline, so it could not find an increased rate of suicidal ideation induction with SSRIs.

The next cited study [24] found a statistically significant doubling of the relative risk of suicide on SSRIs compared with different classes of antidepressants, particularly tricyclic antidepressants. However, the limitations of the study, such as small numbers and selective prescribing, are not mentioned. The authors of this study [24] attempted to explain the differences between SSRIs and tricyclic antidepressants by their finding that less overdose-toxic antidepressants (i.e., SSRIs) were preferen-

tially prescribed to patients at a higher risk of suicide. A similar but larger study [25] also demonstrated a higher risk for deliberate self-harm with SSRIs compared with other antidepressants. The authors again mentioned *preferential prescribing* (more patients on SSRIs had a previous history of deliberate self-harm, and more patients were switched from tricyclic antidepressants to SSRIs than from SSRIs to tricyclics, suggesting that a greater proportion of more 'difficult to treat patients' were prescribed SSRIs) and *age* (patients on SSRIs were younger) as possible limitations of this study and explanations for the differences. This is not mentioned in Healy's [1] article. Another article [26] quoted and recalculated by Healy [1] points out a higher risk of suicide with fluoxetine when compared to other antidepressants. However, some of the antidepressants in the recalculation by Healy [1] have higher suicide rate/100,000 patients than fluoxetine (fluoxetine: 93; trazodone 99; mianserin 166). The authors of this study [26] suggested that selection bias may explain the findings of higher suicide rates associated with fluoxetine in this study.

The last part of this section deals with suicide rate in 'primary care depression'. Healy [1] states that, 'One set of figures stems from Sweden [his ref. 51, here ref. 27], which gives a figure of 0 per 100,000 patients, for the suicide rate in non-hospitalized depression.' Actually, the age-standardized suicide rate per 100,000 person-years in the total Lundby male cohort was 654 for depressive disorder. The article does not mention rates for hospitalized and nonhospitalized depression.

Another example of the 'eye of the beholder' data presentation is an epidemiological study by Simon and Von Korff [28] (Healy's ref. 53). Healy [1] states that the primary care depression treated with antidepressants had a suicide rate of 43/100,000, while primary care depressions not treated with antidepressants had a suicide of 0/100,000. He adds that the possibility that the antidepressant prescribing may have been associated with greater severity (of illness) must not be discounted. One would definitely agree with the latter. In this study [28], the suicide rates are as follows: any psychiatric inpatient: 224/100,000; any mental health specialty visit: 64/100,000; any antidepressant: 43/100,000 and none of the above 0/100,000. It is not clear what none of the above includes, presumably psychotherapy alone, but that is not stated in the article. None of the above category is for 63 out of 850 deaths (none/63 was suicide), while any antidepressant is for 336 out of 850 deaths (8/336 of them were suicides).

National Suicide Rates

Data of Isacson [29], as Healy [1] states, suggest that increased use of antidepressants, primarily SSRIs, has been associated with lowering of national suicide rates. Healy [1] states that there is some evidence from Sweden, but Isacson [29] actually suggests that a similar trend has been also observed in Denmark, Finland and Norway. Healy [1] states that there is contrary evidence to this from Italy and Ireland. However, the cited evidence from Ireland is a previously quoted article by Donovan et al. [24] (Healy's ref. 46 and 57!), which really does not deal with changes of national rates of suicide during antidepressant treatment. It compares data from 222 suicides in three regions, Torbay, England, Northern Ireland, and Cork, Ireland. The article from Italy [30] states that over the 7-year period over which SSRI use increased, male suicide rates increased from 9.8 to 10.2 per 100,000 and female suicide rates decreased from 3.9 to 3.2 per 100,000. Healy [1] further argues that there is certain implausibility to the idea that antidepressant treatment could lower national suicidal rates, citing the article by Hotopf et al. [31]. This article actually addresses the issue of whether SSRIs are a cost-effective alternative to tricyclic antidepressants. It does not discuss national suicide rates and their changes. The authors actually state that suicide is impossible to study in randomized controlled trials. They felt that SSRIs are safer in overdose and if SSRIs cost the same as tricyclic, they would probably become the preferred first-line treatment.

There have been decreases in national suicide rates which Healy [1] does not mention, e.g. the ones mentioned in the letter by Z. Rihmer [3] (see discussion below).

Healthy Volunteer Studies

This part first discusses a study by Healy and his colleagues [e.g., 32, which contains good case descriptions], in which healthy volunteers were administered reboxetine and sertraline. Two healthy volunteers (out of 20), who were given reboxetine and later sertraline, reported suicidal ideation, both while on sertraline. This study generated three references, one of them is a presentation at a meeting. Healy [1] further discusses data on healthy volunteers from studies by pharmaceutical companies, unfortunately without any references (that, especially in view of mentioning 'the suicide of at least 1 volunteer').

A few other studies reported on administration of SSRIs to healthy volunteers [33–35]. Similar to the study described by Healy [32], these studies were not designed to address the issue of suicidality and SSRIs. The first

study [33] focused on sexual dysfunction with fluvoxamine in 20 volunteers and mentioned various other side effects, including nonspecific self-reported psychiatric adverse events. The second study [34] reported no significant effect of fluoxetine on mood, general well-being or quality of life in 15 healthy volunteers. In the last study [35], paroxetine administration reduced psychometric assaultiveness, reduced negative affects, and enhanced social affiliation relative to placebo in 51 volunteers. None of these reports mentioned induction of suicidal ideation, but as mentioned, these studies were not designed to evaluate this issue.

While the data on healthy volunteers might be intriguing, again it is difficult to extrapolate much from them. The numbers are small. Some studies did not report suicidal ideation in volunteers while on SSRIs. It is not clear whether suicidality emerging in nondepressed healthy volunteers could be extrapolated to the depressed patients. It is also not clear whether this reaction is specific to the administration of SSRIs to healthy volunteers. Could healthy volunteers become suicidal during administration of other antidepressants?

Thus, the interpretation of this area of the article again depends on the eyes of the beholder.

Response to Rihmer and Benazzi

In his response to letters by Rihmer [2] and Benazzi [3], Healy [4] again easily discards the arguments of others: '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 ...' Why? Is this a valid argument in a serious debate?

Healy [4] cites a recently published reanalysis of the FDA database by Khan et al. [36]. While he noted that the rates of suicide were lower among placebo-administered patients when compared to SSRI-administered patients (absolute rates: 0.10 vs. 0.15%; suicide rates by patient exposure years: 0.45 vs. 0.59%), Healy [4] does not mention that the SSRI suicide rates were lower than the suicide rates of other antidepressants (absolute rate 0.20%; rate by patient exposure years 0.76%). Even more interesting is Healy's [4] statement about the suicides on placebo in the study by Khan et al. [36]: '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.' Khan et al. [36] only refer to the methods of suicide in each group and

state that only in 1 placebo patient the method was known. They do not discuss whether some patients really did or did not commit suicide. If Dr. Healy has more information regarding the data in this study, he should provide a reference. If he refers to his previous argument about the placebo washout, it would be only fair to restate all numbers, for the SSRIs, other antidepressants, and placebo. Otherwise the debate again points towards the eye of the beholder.

Healy [4] also takes a dismissive stance towards the argument about national suicide rates presented by Rihmer [2]. He states that '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 suggest they might be.' Where is a reference supporting this statement? As I noted in the discussion of Healy's [1] article, the only reference provided does not really address the national suicide rates in the entire Ireland and SSRIs.

New or Other Articles

Hall et al. [37] in their recent article described an association between antidepressant prescribing and suicide in Australia between 1991 and 2000. While the total suicide rate for Australian men and women did not change during this period, there were some age-related differences in the suicide rates. There was an increase in suicide rates in younger adults, especially younger men. There was a marked decrease in suicide rate in older men and women, the groups with the largest increase in exposure to antidepressants. Actually, the largest declines in suicide occurred in the age-groups with the highest exposure to antidepressants across the study period (correlation coefficients were -0.91 for men and -0.76 for women). The authors assume that the increase in prescribing antidepressants has been due to the introduction of SSRIs, though they do not provide any specific data for various antidepressant groups and lump all antidepressants together.

Rihmer [2] mentions his and his colleagues' own work [38] linking the decrease of suicide rates in Hungary during the time of fivefold increase of antidepressant use in this country and times of increased 'social-psychiatric suicide risk factors'. They felt that the increase in the use of antidepressants was a plausible contributing factor to the decrease in the suicide rate.

Finally, in a recent report [39] on a secondary analysis of pooled data from three treatment studies of late-life major depression, the authors did not find that patients treated with either nortriptyline or paroxetine were more likely to experience emergence of suicidal ideation or thoughts with one antidepressant than the other. However, this study had the traditional methodological problems (using the suicide item on the Hamilton Depression Rating Scale; it is unclear whether any of the dropouts – 20.5% – discontinued treatment because of suicidality).

Conclusion

It seems to me that most of Healy's [1] argument contains several if not all mechanisms of good propaganda. Filtering information (selective perception), opinion engineering and marginalization of dissident culture (i.e., contrary opinion in this case) are all present. Does it mean that Healy's [1] arguments are wrong? Not necessarily, but they are at least quite seriously weakened due to the way they are argued.

But what should the reader take out from this debate? There are several points, most of them being unanswered questions, to consider when dealing with the issue of SSRIs and suicide:

(1) Is the syndrome, which SSRIs occasionally cause, truly akathisia (the original term of akathisia, coined a century ago by the Czech psychiatrist Haškovec, meant inability to sit still) observed with antipsychotics, or is it a mild serotonin syndrome? Is it specific to just SSRIs or is the jitteriness [40] observed with other antidepressants something similar? I don't believe that this issue is clearly resolved.

(2) The syndrome of akathisia, restlessness or jitteriness occasionally occurs with SSRIs. However, we do not know if it always leads to suicidality and what the relationship between this syndrome and suicidality is. Also, we cannot assure ourselves that this syndrome is unique to SSRIs and that the relationship between this syndrome and suicidality (if there is a relationship) is unequivocally specific to SSRIs. Whether or not it is specific to the SSRIs, we need to clarify why only a few patients suffer from it while most do not. Were the Soviet Union dissidents, rumored to be administered psychotropics to induce akathisia or restlessness, also suicidal? Also, is akathisia, restlessness or jitteriness undergoing a 'natural' reporting cycle of many side effects of various drugs, i.e., going from high reporting to almost no reporting (at present) to occasional reporting?

(3) How do we identify, prior to the exposure, the individuals, which Healy suggests are vulnerable to this syndrome?

(4) Suicide is a serious, rare and poorly understood phenomenon. The present methods of examining suicide and its possible association with antidepressants in clinical trials are inadequate. Most of the methods used to study the frequency of suicide in the article are insufficient and even their sum is, in this case, not fully convincing at the best. There are numerous factors unaccounted for in any analysis. Just a single issue of the *American Journal of Psychiatry* (April 2003) contains three articles [41–43] on suicide risk factors, mentioning even prevailing levels of bright sunlight [42] and cigarette smoking among the risk factors [43].

(5) Psychological autopsies of suicides in trials could be very helpful.

(6) We need to design new studies for studying this phenomenon (is there a design which could address this that would be ethical?).

(7) We need to reanalyze all the available data without any preconceived ideas.

(8) Is statistical evidence enough for lines of evidence and causality in this case?

(9) Last but not least, we need to read articles critically (including the one you just finished reading).

I forewarned the reader that there is no definite answer to the question whether SSRIs specifically trigger suicidality. At the present time, the evidence seems to be in the eye of the beholder. However, this important issue should not be totally discarded and requires further, better, analysis.

We need to be cautious and wary about the effects of any kind of propaganda. The issues discussed by Healy are important, yet the implications, in view of the misinterpretation of data and filtering information, dangerous. One of the possible effects of this propaganda might be the avoidance of effective treatment by depressed patients and their physicians. That would be an undesirable and harmful result which, hopefully, nobody wants. Finally, if Healy's warning breeds true, another remaining issue is whether SSRIs and other antidepressants should be used by primary care physicians as freely as they are, or at all.

Competing Interests of Richard Balon, MD

In my professional lifetime, I have been a principal investigator, coinvestigator for studies and speaker or member of advisory boards of the following pharmaceutical companies: Boehringer Ingelheim, Bristol-Myers Squibb, Ciba-Geigy, Eli Lilly, Forrest, Glaxo (now

GSK), Novartis, Parke-Davis, Pharmacia-Upjohn, Organon, Pfizer, Roche, Sandoz, Smith Kline Beecham, Solvay, TAP, Upjohn, USB Pharma, Wyeth. I am sure I received free lunches from others.

I do not testify as an expert witness.

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