Journal of Psychiatry & Neuroscience

Revue de psychiatrie & de neuroscience

cma.ca/jpn

January 24, 2003

David Healy, MD
Department of Psychological Medicine
University of Wales College of Medicine
Hergest Unit
Bangor
UNITED KINGDOM LL57 2PW

FAX: 011 44 1248 371397

Re: **Antidepressant Use and Suicide** (Point-Counterpoint Feature: **July** 2003)

Dear Dr. Healy:

Please find attached for your consideration a copy of Dr. Yvon Lapierre's manuscript on antidepressant use and suicide. As discussed, this manuscript will run alongside yours as part of a "point-counterpoint" feature in the *Journal of Psychiatry & Neuroscience*. While we hope to publish this timely feature in our May 2003 issue, we have listed a July publication date above to allow for unforeseen delays.

Should you wish to respond to Dr. Lapierre's arguments in the body of your manuscript, please feel free to do so. We will, of course, require a revised version of your text for our files once it is ready.

Please feel free to contact me should you have any questions or concerns about this material.

Yours sincerely,

Ms Megan Sproule-Jones
Managing Editor

A.V.HEALY.WPD

Canadian Medical Association
Association médicale canadienne
Publications Directorate
Direction des publications
1867, prom. Alta Vista Drive
Ottawa ON K1G 3Y6
Canada
telephone/téléphone: 613 729-9545
fax/télécopieur: 613 729-9545
email/courriel: jpn.office@sympatico.ca

Journal of Psychiatry & Neuroscience

Revue de psychiatrie & de neuroscience

cma.ca/jpn

15 APR 2003

April 9, 2003

David Healy, MD
Department of Psychological Medicine
University of Wales College of Medicine
Hergest Unit
Bangor
UNITED KINGDOM LL57 2PW

Re: **Antidepressant Use and Suicide: Risk-Benefit Conundrums** (Point-Counterpoint feature: manuscript A)

Dear Dr. Healy:

I am pleased to inform you that your manuscript has now been reviewed by two experts in the field. After carefully considering their comments, the Editorial Board has determined that your paper will require revision and further review before it can be considered for publication in the *Journal of Psychiatry & Neuroscience*.

For your information, I have enclosed the reports of both referees. As you will see, they have provided comprehensive and thoughtful assessments of your manuscript and, given the controversial subject matter, have raised important concerns about the strength and structure of the arguments in the point-counterpoint feature as a whole. While we hope that you will revise your paper taking into account their suggestions and concerns, we recognize that such revisions may be extensive and perhaps, indeed, prohibitive.

Should you be willing to take up this challenge, please send **four copies** of your revised manuscript along with a letter detailing the changes made and your responses to the suggestions of the referees, including page and line numbers of changes to the text. If possible, **please include a copy of your revised manuscript on diskette** and list the file names and types on the attached form. Ideally, we would like to receive your revised manuscript within **two months** so that we may reactivate the review process promptly.

Thank you again for agreeing to submit a manuscript for our point-counterpoint feature, and for your patience during the review process. Please rest assured that the *Journal* remains committed to providing its authors with a timely, fair, and thorough assessment of their work.

I look forward to reading your revised manuscript in the coming weeks.

Yours sincerely,

Russell T Joffe, MD
Co-Editor-in-Chief
Encl.

Canadian Medical Association
Association médicale canadienne
Publications Directorate
Direction des publications
1867, prom. Alta Vista Drive
Ottawa ON K1G 3Y6
Canada

telephone/téléphone: 613 729-9545
fax/télécopieur: 613 729-9545
email/courriel: jpn.office@sympatico.ca

Dear Dr. Joffe,

Re : Antidepressants and Suicide: Risk-Benefit Conundrums (Manuscript A)
Suicidality with SSRIs: A Valid Claim ? (Manuscript B)

You have correctly identified this as a controversial topic. Both Drs. Healy and LaPierre come from different backgrounds with different perspectives. (I am careful not to use the word 'biases'). The approach they use to present their case or arguments is quite different. Dr. Healy follows a rather detailed if not nitpicking approach. He argues for ignoring or excluding segments of studies (or even entire studies) often, but not always justifiably. He does so in order to advance what appears to be his case. And yet after having done so in a painstaking manner and with what appears to be a lot of conviction he adopts a conservative position in his rather brief and parsimonious concluding remarks.

Dr. LaPierre uses a broader brushstroke to paint his picture and his contribution is still concerning pharmacotherapy. He ignores or dismisses some of the studies and data presented by Dr Healy but with few exceptions he does so in general terms as if he decided to ignore or perhaps has not had a chance to review the Healy-Whitaker manuscript. At the end, however, in his concluding remarks, he seems to rather agree with Dr Healy's conclusions i.e. that "any conclusion based these few reports of rare sporadic cases of increased suicidality with SSRIs must be limited and highly tentative" and that "a tailoring of the total profile of the drug can by applied to the clinical profile of an individual patient" or as Healy and Whitaker argue "particular personality types suit particular selective agents".

So the questions arises as to what is the purpose of this point-counterpoint presentation Perhaps we should also ask the questions if this is a debate, who wins the debate. D LaPierre, of course, will satisfy the plethora of clinicians who will see in his paper an conclusions a confirmation of their beliefs and practice. It will also please th pharmaceutical industry out those associated with it. I suspect many will find th nitpicking approach of Dr Healy tiresome and perhaps suspect that he does have an axe t grind, skip most of the article and go directly to the conclusions in which they will fin reassurance. Some clinicians and those with a science background however will pay undoubtedly close attention to what Dr Healy has to say within the text and the figures o tables and discover (as I did) the incongruity between the text and conclusions. The tex (unlike his concluding remarks) represents a definite effort to demonstrate that the risk o "suicidality", suicidal acts and suicide is higher in patients treated with SSRIs (see for example page 4 last paragraph, page 5 paragraph 2 and 3, and table 4).

The problem I foresee is that some, and perhaps many, will take exception to Dr Healy's numbers and ratios in the text and raise questions as to his methodology. The counterpoint paper by Dr LaPierre failed to scrutinize Dr Healy's arguments and figures as presented in the Healy-Whitaker manuscript. It is therefore my suggestion, if not too late, that instead of a point-counterpoint presentation to forget about Dr LaPierre's paper as such (it does not offer for a sound review of the approach and methodology followed by Healy and Whitaker) and to have Dr Healy's article stand for review on it's own merit. Of course it will have to be reviewed especially by those familiar with this topic and by those who possess expertise in meta-analytic methodology. If then you decide to accept Dr. Healy's paper, you could always have an accompanying guest editorial or letter(s) published simultaneously that will express any remaining differences of opinion between Dr Healy, the reviewers and perhaps the Editor(s).

JOURNAL OF PSYCHIATRY & NEUROSCIENCE

REFEREE FORM II

REFEREE # 2

Manuscript Number: Point-Counterpoint Manuscript A

Manuscript Title: Antidepressants and Suicide: Risk-Benefit Conundrums

COMMENTS FOR THE ATTENTION OF THE AUTHOR (CONTINUE ON A SEPARATE SHEET IF NECESSARY):

Antidepressants & Suicide: Risk-Benefit Conundrums
David Healy

This paper puts forth the argument that antidepressants are associated with increased suicide risk compared to both other antidepressants and no treatment.

The author states on page 4 that Khan et al., 2000 "found an excess of suicidal acts on antidepressants compared to placebo…". The Kahn paper, however, states "The differences in suicide rates did not reach statistical significance" and "the differences in rates of suicide attempts did not reach statistical significance" for investigational antidepressants and comparator antidepressants compared to placebo. Furthermore, the Kahn paper uses a LOCF and the author argues that those suicide and suicide acts that occur during the placebo washout period don't count, an argument that appears less than cogent. The author then removes the suicide washout data then reanalyzes the data and then states odds ratios of suicidal acts and completed suicides compared to placebo. For unexplained reasons, the statistical significance for the odds ratio is given for paroxetine only. The results are presented as odds ratios, which inflate rather small differences for low prevalence rates. For example, in Table 1, the rate of suicides and attempts for all SSRIs = 1.53% and for SSRI trial placebo = 0.57%; the 95% CI for this difference is between .6% and 1.2%; but no statistical significance is provided.

The author also states "Kahn et al found an excess of suicidal acts on antidepressants compared to placebo, which has been replicated in two other analyses (10,11)". The #10 reference, Storosum et al., 2001, shows in 77 studies done in the Netherlands, 4/4,302 (0.1%) patients treated with placebo committed suicide compared to 7/7,944 (0.1%) patients who were treated with antidepressants; 17/4302 (0.4%) of the placebo group and 29/7,944 (0.4%) of the active group attempted suicide. Similarly, in long-term studies, no difference was found between the groups. In Medline long-term studies, seven withdrawal studies found one that had more suicide attempts in the antidepressant group but no difference was found in the rest of the studies. This reference fails to support the author's assertion that an excess of suicide acts were found with the antidepressant group.

The author then goes on to criticize the analyses done by Lilly in response to the Teicher paper. Here, again, the arguments marshaled are less than cogent. The argument that the trials were not designed to test whether or not fluoxetine could be associated with suicidality could just as easily apply to all of the other data presented by the author. The author states that Lilly used only a selected subsample, but does not provide any source or explanation of this assertion. The author states that benzodiazepines could have been prescribed to minimize agitation, but does not state how frequently this was done. If 5% of the patients dropped out because of anxiety/agitation, this does not mean that these patients were suicidal as implied by the author. Instead, the author makes a connection stated in the DSM. The argument that the HAMD would not pick up exacerbated suicidality because "clinicians [were] not aware of this possible adverse effect" is specious at best.

The author then makes the statement "the claim that SSRIs reduce suicidality in some patients appears strong", essentially damning this claim with faint praise while failing to provide any data or references supporting this statement. This could have the appearance of bias, such that data is provided to support one's argument while minimizing data that might be contrary.

One gross omission is the possibility that those who possibly did become either suicidal or committed suicide with antidepressant treatment were, in fact, not unipolar, but instead bipolar. Those depressed bipolars unmedicated with a mood stabilizer who are treated with an antidepressant can become agitated with a mixed state or antidepressant induced mania or hypomania. Goldberg et al., 2001 found that up to 45% of patients hospitalized for depression ultimately declared themselves as either bipolar I or II. This point would strengthen the paper and lead clinicians to improve practice.

The epidemiological evidence presented is far from convincing. Here, the data are subject to susceptibility bias, specifically that those who would be at most risk of suicide in the community would most likely be prescribed those antidepressants least likely to cause death by overdose. Furthermore, the data do not allow one to know if the patients prescribed SSRIs had already failed to respond to tricyclics, particularly during the first 5 years after the SSRIs were introduced into clinical practice. The strong possibility of susceptibility bias undermines the author's interpretation of both the Jick et al. data and the comparison between treated and untreated depression in primary care. No mention is made that while an association may exist between SSRIs and suicide in this epidemiological data, cause and effect cannot be determined because those data are not available that compares baseline data of patients treated with SSRIs vs. other antidepressants. Similarly, it does not appear helpful to compare the suicide rates of treated vs. untreated depression – those with more severe depression (and greater baseline risk of suicide) would be more likely to be treated. It would be akin to saying that in a naturalistic study, those patients with coronary artery disease who receive surgery have better outcomes than those who receive medicines alone – ignoring the fact that patients are rejected from surgery if they are too sick to survive the surgery. In other words, the

surgical group and the medical group had different susceptibilities to the outcome of interest.

Data that shows this possible susceptibility bias can be found in Table 3 of Leon et al.'s 1999 paper (reference #28 in the reviewed paper). In this prospective naturalistic study, 185 patients who received fluoxetine were compared to 226 patients who received other antidepressants and 232 who received no antidepressants. The fluoxetine group had more affective episodes before intake (3.4 vs. 2.5 vs. 1.6 respectively, $p < 0.001$), no statistically significant differences in the proportion who attempted suicide in the year before intake (20.5, 23.1, 29.6% respectively), more prospectively observed episodes (2.4, 2.1, and 1.3 respectively, $p < 0.001$), and more likely to have attempted suicide prior to the introduction of fluoxetine (36.2, 27.4, and 25.4% respectively, $p = 0.04$). When a multiple mixed effects model corrected for the differences in baseline risk, fluoxetine was not associated with increased risk of suicide. Interestingly, the author of the reviewed paper dismisses the Leon et al. paper as having too few patients and falling short of an epidemiological paper.

JOURNAL OF PSYCHIATRY & NEUROSCIENCE

REFEREE FORM II

REFEREE # 2

Manuscript Number: Point-Counterpoint Manuscript B

Manuscript Title: Suicidality With SSRIs: A Valid Claim?

COMMENTS FOR THE ATTENTION OF THE AUTHOR (CONTINUE ON A SEPARATE SHEET IF NECESSARY):

Suicidality with SSRIs – valid claim
Yvon D. LaPiere

This paper is a counterpoint to the companion paper by Healy. The author argues that one must be cautious when interpreting the data that suggests antidepressants may cause suicide or suicide attempts.

The author states that the risk of suicide has remained around 15%, but at least for depression, this is probably a gross overestimate and reflects the suicide rate of patients hospitalized for depression over 25 years ago (see Guze et al.).

No mention is made about susceptibility bias in epidemiological studies. This concept is, however, referred to obliquely on page 5, 3rd paragraph.

No mention is made about the misdiagnosis of bipolar disorder in patients who present with depression; antidepressants can exacerbate this group in the absence of mood stabilizers.

On page 8, last paragraph, the author discusses the work of Kahn et al., stating that only 48% of studies show that active antidepressants are superior to placebo. This should be updated with the more recent data presented by Kahn that 60% of studies show superiority of antidepressants when flexible doses are used.