

Tuesday, August 13, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3374-editedRowan).

Title: Does prophylactic antidepressant treatment boost interferon-alpha treatment completion in HCV?

Author: Paul J. Rowan

Name of Journal: *World Journal of Virology*

ESPS Manuscript NO: 3374

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) The results part in the abstract is weak: where are the results from.

Upon receiving this criticism, I see that I did not explain in the abstract how I analyzed the studies. I have now included this information. This is highlighted in the revised manuscript.

(2) Are there all studies mixed no matter what design?

I went ahead and reviewed whether all results were mixed, no matter what design.

There were 9 studies with data that permitted a Fisher's Exact Test to test whether the discontinuation rate differed between prophylaxis arm and rescue arm. Of these 9, only 4 had results that were statistically significant. Three modestly favored prophylaxis. These were: Diez-Quevedo et al 2010 (7.8% discontinuation in prophylaxis arm, 12.5% rescue arm, Fisher's $p = .02$), Neri et al 2010 (8.5% discontinuation in prophylaxis arm, 10.5% discontinuation in rescue arm, Fisher's $p = .02$), and Raison et al 2007 (0.0% prophylaxis arm, 33.3% rescue arm, Fisher's $p = .02$). The one study favoring rescue was Liu et al 2010 (47.8% discontinuation in prophylaxis arm, 8.0% discontinuation in rescue arm, Fisher's $p = .02$). With five studies having no statistical difference in discontinuation, three favoring prophylaxis by varying portions, and one favoring rescue by a strong portion, there seems to be no consistent pattern favoring either strategy. This addresses the issue of whether all studies are mixed, no matter what design.

These analyses have been added to the manuscript. This is highlighted in the revised manuscript.

(3) What was the reason for discontinuation? Was it depression?

This is a great question, but cannot be fully analyzed since the data in the studies is varied, and limited. To the extent possible, I have analyzed reasons for discontinuation. I have added these analyses to the manuscript, and have also added Table 2, which conveys the available data in tabular form.

This addresses the issue of reason for discontinuation. This is highlighted in the revised manuscript.

(4) In the introduction and discussion the following questions should be answered:
What is the link of depression and immunology?

This is a complex issue. There are many lines of thought, and lines of evidence, but there is not yet a consensus. Generally, it is thought that when immune responses happen, the pro-inflammatory cytokines play a mood/affect role as well as an inflammatory response/infection-fighting/healing role. The brain may register these cytokines, and induce a pattern of symptoms described as "sickness behavior." This includes a desire to sleep, anhedonia, and other symptoms that parallel depression. The theory is that this demotivation serves as a resting period, permitting better healing.

In the discussion, I have added information about the link between depression and immunology, with supporting references. This is highlighted in the revised manuscript.

(5) Why do they patients get depression under Interferon-Alpha Treatment?

IFN-alpha either may lead to this "sickness behavior" phenomenon itself, or other cytokines prompted by IFN-alpha therapy may lead to the "sickness behavior" phenomenon when provoked by the IFN-alpha. I have added discussion and references concerning this to the manuscript. This is highlighted in the revised manuscript.

(6) Why do SSRI help?

This is not clear, but it is believed that the SSRIs somehow modulate the "sickness behavior" of pro-inflammatory cytokines. I have included a brief discussion about this in the manuscript, and a supporting reference: Janssen 2010. This is highlighted in the revised manuscript.

(7) Why is discontinuation rate not getting better under SSRIs?

This was addressed in the manuscript. An additional sentence has been added to add more emphasis to this point:

"Why didn't the prophylaxis approach have superior treatment completion, along with superior

depression management, compared to rescue approach? It is possible that, in these trials, the rescue strategy worked as well as prophylaxis because clinical trials often have clinical management practices (answering patient questions, establishing clear lines of communication, systematic symptom monitoring, recruitment of motivated patients) that is stronger than usual care. If this is the case, then those delivering interferon-alpha treatment for chronic hepatitis C should be sure to parallel the symptom monitoring strategy of these trials. The monitoring of depression is a topic that has already been covered well in the literature concerning antiviral therapy, and has long been incorporated into treatment guidelines."

This is highlighted in the revised manuscript.

3 References and typesetting were corrected

Thank you again for publishing this manuscript in the *World Journal of Virology*.

Sincerely yours,

A handwritten signature in dark ink, appearing to read 'Paul J. Rowan', is centered below the text 'Sincerely yours,'. The signature is fluid and cursive.

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