

Barcelona, 23th December 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: review.doc).

Title: Brain-derived neurotrophic factor levels in first episode psychosis: a systematic review.

Author: Alba Toll, Anna Mané

Name of Journal: *World Journal of Psychiatry*

ESPS Manuscript NO: 14373

We thank the reviewers for their helpful comments. 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

Reviewer 1.

In Conclusions of Abstract and Discussion sections it should be important to include the need for a future meta-analysis in this topic.

We have added the need for a future meta-analysis in this topic in the abstract and discussion.

Results section should be expanded and part of the Discussion section needs to be moved there.

We have expanded the results section and moved part of the discussion there.

A reference to an original article demonstrating that BDNF protein crosses the blood-brain barrier should be included.

We have added this reference in the manuscript (Sartorius et al 2009).

There was statistical significance for the difference in sex distribution for the studies that were positive and negative for BDNF reduction? An exploration of the possible effect of sample sizes of included studies should be important.

We have considered the effect size and we have not seen any possible gender effect, as we have mentioned in the discussion. (Correlation percentage of males and effect size : $r=-0.025$, $p=0.936$)

Authors should check coherence between citation numbers in Table 1 and references. For example, the reference 15 in "Yoshimura 2012[15]" corresponds to Sotiropoulou et al 2013.

We have now revised all the references.

Size effect should be included for the reported changes described in last column of Table 2.

We have included it.

Data for BDNF levels in Table 2 should be converted to the same scale (for example ng/ul).

It is not clear why in Table 1 and 2 some studies appear as FPE subjects receiving medicaments. For example,

Yoshimura 2012 provides BDNF data for "first-episode untreated Japanese schizophrenia patients". Authors should check and correct data for all included studies.

We have explained the tables more appropriately.

Reviewer 2.

The authors should include a rationale to why they included only studies that reported enzyme-linked immunosorbent assay measurement.

We have included only these studies because enzyme-linked immunosorbent assay is the gold standard measurement for BDNF levels in serum or plasma. We have also referenced it in the methods.

Did the authors verified the samples used in the selected studies? Some FEP patients could have been recruited immediately after or during the acute phase, whereas other studies could have waited for stabilized patients. This would come in contradiction with their hypothesis of FEP as a less heterogeneous sample. Could this be an issue worthy for discussing?

We could not get data from all the studies regarding the exact moment BDNF was measured, although most patients were in the acute phase before taking antipsychotic treatment. We agree that this fact could make the sample less homogenous, and we have corrected that point in the last paragraph of the introduction and have considered it in the discussion. "Patients clinical characteristics could also affect BDNF levels...".

First, the authors might have wanted to develop their interpretation that "that antipsychotic medication contributed to the inconsistencies in BDNF levels in previous reports". For instance, is it plausible hat medication might have normalized BDNF levels in FEP? Could they not have analyzed/interpreted the data from the studies that reported BDNF levels before and after antipsychotic treatment in this regard?

We have developed this interpretation, and added the plausible explanation that medication might have normalized BDNF levels, adding some references about studies consistent with that explanation. However, analyzing the data from the studies that reported BDNF levels before and after antipsychotic treatment was beyond the scope of this systematic review.

Stating that "the mean age in the studies that found lower BDNF levels in patients than those that did not was not statistically significant" is a result. It should not be in discussion. The interpretation, however, should state that in Green et al. (2011), the age difference between drug-naive patients and medicated patients was around 10 years, vs only 3 years in the present study (and a non-significant age-difference). This might account for the lack of difference in BDNF levels noted by the authors. Knowing whether the studies that found or did not find differences had enough statistical power to do so would be important for the reader.

We have moved "the mean age in the studies that found lower BDNF levels in patients than those that did not was not statistically significant " to the results section and have discussed differences regarding age between Green et al (2011) and our study.

We have also added the effect size and confidence interval in table 2 to help the readers.

The authors state that: "The percentage of men in the studies included in this review was 52.18%, and was lower in the studies that found decreased BDNF levels in patients compared to those that did not (50.10 vs. 57.36%)." This is actually congruent with Green et al. and should be discussed: Green et al observed that finding a BDNF reduction in males was dependent on excluding an outlier study. When excluding it, both males and females had lower BDNF levels.

We have added this consideration in the discussion section. We have modified the exact percentage as there was a mistake.

Page 6: The authors state: "Further research should therefore be performed to clarify the effects of cannabis use on BDNF levels in FEP patients."

Since the authors have excluded from their systematic review the articles tackling the issue of BDNF Val66Met, they should at least discuss the fact that drug abuse might have differential effects according to the polymorphisms implicated. A short Medline research already provided some clues that cannabis might have a different impact on BDNF Val66Met carriers.

We have added the fact that drug abuse might have differential effects according to the polymorphisms implicated in the discussion section.

Another point could be to briefly discuss the timing of BDNF reduction: is the reduction installed before disease onset (in the CHR, for instance) or following the first episode?

Most of the studies were carried out in the acute phase in neuroleptic naïve patients before treatment was given. However we do not know the exact time BDNF was extracted regarding the episode, and we have briefly discussed it in the discussion. A future research in patients at high risk would be very interesting to clarify this issue.

Environment such as early life adversities could also play a role and account for discrepancies between studies
We have briefly discussed this factor in the discussion.

Even if this issues are beyond the scope of the review, it would give the reader a better idea of the context of BDNF lowering.

We have briefly included it in the second paragraph of the introduction.

The patients should add as a limitation their overlooking of BDNF polymorphisms, that are widely acknowledged as important factors in neuropsychiatric disorders.

We agree that BDNF polymorphisms are important factors in neuropsychiatric disorders and we have added this limitation in the limitations section.

Page 4. The sentence in the last paragraph before ?Methods? should be rephrased by précising the meaning of a "homogeneous sample". The authors should take care of using of homogeneity in the disease, since it is a wide notion. I suggest " FEP patient presentations may be more comparable in terms of illness duration, etc.

We have reconsidered it and rephrased it.

When the authors state that "Indeed several studies have been carried out to particularly adresss this issue" references are needed. Otherwise if these studies are precisely the ones that are the core of the present systematic review, perhaps modify the sentence to make it clear to the reader.

As these studies were the ones that are the core of the present systematic review, we have modified the sentence to make it clear to the reader

Results section: The authors should add at list one sentence to summarize the results. Such as the first sentence of the discussion that could be placed here.

We have added this summary in the results section.

Page 6: The authors state " Although they did not find differences in BDNF levels between schizophrenia patients and controls that were non-users, serum levels were significantly increased in schizophrenia patients that used

cannabis compared to cannabis non-user patients and controls, which was different from the results of a more recent study”

These sentences are confusing. I understand what the authors mean, but they certainly could simplify their thinking. In a nutshell, Jockers-Scherubl observed that cannabis-consuming patients had than non-user patients and controls?

We agree it is a complex sentence and we have redone it.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Psychiatry*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Alba Toll Privat', with a stylized flourish at the end.

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