Response to reviewer comments

ESPS3608, Cannabinnoids limit axonal damage and prevent neurodegeneration in multiple sclerosis.

Dear Professor H. H. Zhai,

Thank you for the reviews for the manuscript with the above reference number and title. In the revised version of the manuscript all of the improvements suggested by the reviewer has been included. All changes have been highlighted using the track changes function in Microsoft Word. The responses to specific comments are below:

1. "*Better use of headings to guide the reader through the manuscript – with a particular emphasis on developing the idea that CB receptor pharmacology is a useful potential target for MS treatment.*"

More headings have been used and I have now developed the idea of CB receptor pharmacology and its usefulness in MS.

"*There are some important papers that provide solid evidence around this issue are not cited. In particular the work of Centronze et al Brain 2007 which show direct links between dysregulation in the cannabinoid system and EAE and human MS.*"

I have generally included more references in the manuscript but the particular studies mentioned by the reviewer have been included.

2. "*Better description of the various models of MS that have been used to stud the role of cannabinoids; particularly with respect to their advantages and disadvantages. Other animal models of MS (eg the TMED-IDD model) also provides useful evidence that modulators of cannabinoid inactivation may have therapeutic benefit (eg Mestre et al 2004 Journal of Neurochemistry).*"

I have described the other models of MS and have discussed their advantages and disadvantages.

3. "*More discussion about the controversial role of cannabis in MS clinically (on page 5 comment is made about the uncertainty, from clinical trials, as to the beneficial effects – it would good to expand this a little and provide some discussion about whether animal models of MS might shed additional light on the way forward for human trials.*"

Discussion has been added regarding animals models of MS and what contribution they play in terms of MS research.

4. "*A better connection between how mechanisms of axon damage in MS and models of MS may be informed by studying the endocannabinoid system.*"
This has been clarified in the relevant sections.

Minor points:
(i) "*There is a need to define abbreviations and other terms on first usage. For example CREAE appears in the abstract without definition and Sativex is referred to on Page 5 two sentences before there is an explanation as to what it is.*"
Abbreviations have been defined on first use.
(ii) "*The data from reference 14 is somewhat loosely reported as I could not find any specific reference to improvement in sleep problems for 88% of patients.*"
Reference to sleep improvement has been deleted in terms of reference #14.
(iii) "*The abstract could be shortened and focused on what the review brings to the reader in terms of new information. I suggest that you amend the sentence: "We show that ....." because in this article you haven't really shown this at all – what you have done is provided evidence from already published literature) to support the contention that...*"
Abstract has been shortened and "We show that" term has been changed to "we reported that"
(iv) "*On page 4 para 2: its use is illegal (it's shouldn't have an apostrophe).*"
Amended.