Reviewer

The work is correctly documented in the updating of clinical trials, a minimum of data on the justification for the use of different therapeutic methods and a correct analysis of the statistical comparisons. A complete description of the different therapeutic approaches to HE.

Thank you for your kind words.

Concerns The main one is that the work must delve into the pathophysiology of HE, if not, the basis of the different treatments will be related only to the mechanisms of the drugs and not to the basis of the molecular pathways of ammonia. The authors said that "the pathogenesis of HE is a multifactorial entity with numerous mechanisms that results in functional impairment of neuronal cells, none of which is clearly understood." This paragraph is incomplete. Explain the basic pathways of HE; otherwise, there is not enough support for therapy. See pathophysiology information. I agree that it is a "disease caused by multiple factors", but there are important pathways already described, for example. The Trojan theory of Noremberg et al., Which highlights the mechanism that involves the mitochondrial pH of astrocytes. So again, the pathophysiology must be described, at least mentioned because it is basic to the rationality of therapy. Also, it's not just neurons that are involved in HE, see the references regarding astrocytes as they have the machinery to metabolize ammonia. The blood-brain barrier (BBB) must also be considered, it is the main target of hyperammemia and the consequences of altered permeability of the BBB also define the development of HE. Following this point of view, pathophysiological arguments are needed, the reader might ask: if cirrhosis is the main cause of HE, and in cirrhosis a state of sarcopenia is described, how can ornithine phenylbutyrate improve the activity of skeletal muscle to purify ammonia? Figure 1 should be redesigned. The HE classification is already known, so fig. it is very large, it does not integrate information. The authors state that "The pathogenesis of HD is a multifactorial entity with numerous mechanisms that result in functional impairment of neuronal cells, none of which is clearly understood" and cited reference # 3, authors should include reference # 19, and a new one may be included.: Definition and

nomenclature of hepatic encephalopathy by N. Dharel and J. Bajaj can be consulted in (J Clin Exp Hepatol. 2015 Mar).

Thank you for your comment. We have dedicated a paragraph for the the pathophysiology of hepatic encephalopathy and we have added a detailed figure, figure 1 with a description that highlights the different pathophysiological mechanism involved.