

Preventing the sequelae of concussions and traumatic brain injury

Keywords: Lithium, Neuroprotection, Traumatic brain injury, Valproate

Abbreviations: IED, Improvised Explosive Devices; Li, Lithium; NAC, N-Acetyl Cysteine; NFL, National Football League; TBI, Traumatic Brain Injury; VPA, Valproate

Letter to Editor

The American Academy of Neurology guidelines on concussions and traumatic brain injury (TBI) presented at the Academy's Annual Meeting and published in March 2013 are of considerable interest and importance. In addition to the informative material in the guidelines, we would propose the addition of one critical dimension: potential treatment interventions.

There are many possible, safe interventions with evidence of neuroprotective effects in animal models of TBI, stroke, and other neurodegenerative conditions. Randomized clinical trials in athletes utilizing some of these agents should be undertaken as soon as possible to evaluate both short-term and particularly long-term outcomes.

The evidence is already clear that repeated concussions increase the risk of cognitive dysfunction and other behavioral disturbances.¹ The field should today begin to address what might prevent these long-term disabilities so that another generation of athletes and those suffering head trauma in accidents do not emerge without attempts at prevention of dysfunction and disability.

A randomized study of acute administration of the mood stabilizers lithium [Li] and Valproate [VPA] compared to placebo would be an excellent start as both drugs have demonstrated positive effects such as neuroprotection, anti-inflammation and behavioral/cognitive improvements in stroke and TBI, and have shown evidence of additive or even synergistic effects in combination.²⁻⁶ Notably, Li and VPA are already extensively used and well tolerated in clinical settings for bipolar disorders, and their beneficial time windows in preclinical studies of neuroprotection are most intriguingly up to several hours after the brain injury.

If, for example, a pro-football player is taken off the field and meets criteria for a concussion sufficient for removal from the game, he could be randomized to several days of treatment with the Li + VPA combination in comparison to placebo. Players giving informed consent in advance would greatly facilitate the study, and avoid possible compromise of the consent process because of the concussion. Acute and subsequent longer-term testing would rapidly assess whether the active intervention were effective.

Other completely safe, non-prescription drugs should also be tested. For example, there is preliminary evidence that the benign, over-the-counter medication, N-Acetyl Cysteine [NAC], which has antioxidant, anti-inflammatory, and anti-glutamatergic effects, may have positive effects in TBI.⁷ If the initially studied agents proved

to be ineffective, a series of new randomized comparisons based on studies in animals could be initiated.

Similar randomized studies could also be performed in emergency rooms on head trauma patients able to give informed consent. Regrettably, the uniformed services may have missed an ideal time to assess possible acute interventions when so many soldiers in the Iraqi and Afghanistan campaigns were being exposed to the head trauma associated with road side and other improvised explosive devices [IEDs]. Thus, we currently know little about primary and secondary prevention.⁷ The logistics of planning and conducting such studies may possibly be even more complicated in the NFL than in the military, but could be overcome by all involved (players, owners, and scientific investigators) seeing critical questions answered, and their altruism and self interests enhanced.

Players, we believe, would especially readily agree to such potential studies in the hopes of eventually identifying successful interventions. Both the players union and the owners in the NFL would likely see the merits of such investigations.

Acknowledgements

Both authors contributed equally to this manuscript. De-Maw Chuang was supported by the Intramural Research Program of the National Institute of Mental Health, National Institutes of Health.

Conflicts of interest

This work was written as part of De-Maw Chuang's official duties as a United States Government employee. The views expressed in this article do not necessarily represent the views of the NIMH, NIH, HHS, or the United States Government.

Volume 2 Issue 1 - 2015

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Received: November 25, 2014 | **Published:** January 03, 2015

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