

## Letter to the Editor

We applaud the efforts of the American Academy of Neurology to provide rigorous reviews of the literature to critically assess the evidence supporting diagnostic methods and therapies for neurological disorders. However, we are concerned that use of Type I evidence only and the practice parameters as provided in this paper may be misinterpreted by patients, federal agencies, practitioners and insurance companies that the absence of evidence from randomized, double-blind, controlled trials implies a lack of efficacy. The update of plasma exchange for neurological disorders concluded that evidence for the application of plasma exchange for myasthenic crisis and treatment prior to thymectomy merits a Level U recommendation.<sup>1</sup> For myasthenia gravis, and many orphan diseases, randomized placebo controlled studies are difficult to design and perform for numerous reasons; these include ethical concerns based on standards of care, lack of federal funding, absence of economic incentives for industry sponsorship, poor infrastructure for performance of trials, and the challenge of coordinating clinical trials for a rare condition.<sup>2</sup> Furthermore, widely accepted standards of care may prompt medical ethics boards to deny approval of placebo control arms in clinical trials, and until alternative therapies can be used as active comparators in superiority studies, advocating the Level U in this instance could do harm. We do not disagree that there is a lack of placebo controlled trials of plasmapheresis in MG. However, in the case of plasma exchange, there is a consensus worldwide that the treatment is rapidly effective for myasthenic exacerbation. The preponderance of clinical experience and published observation rises to a level that argues against the need for a randomized trial which includes a placebo (sham exchange group). Many would view such a trial design to be unethical for patients in myasthenic crisis, since treatment failure could mean death. We are reminded of the tongue in cheek article published in 2003 of the lack of randomized controlled trials of the parachute.<sup>3</sup> We think this point should have been made in the choice of parameters used to judge treatments. While we recognize that further investigation is needed to improve treatment of MG, a randomized, sham-controlled trial of plasma exchange, while ideal from an academic perspective to satisfy Type 1 evidence criteria, would be virtually impossible to conduct, would not be in the best interests of patients, and would likely place other important therapy questions in the field of MG on hold.

Henry J. Kaminski, MD

Gary Cutter, PhD

Robert Ruff, MD, PhD

Gil Wolfe, MD

The appendix contains names of individuals who indicated agreement with the contents of this letter

## References

1. Cortese I, Chaudhry V, So YT, Cantor F, Cornblath DR, Rae-Grant A. Evidence-based guideline update: Plasmapheresis in neurologic disorders: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2011;76:294-300.
2. Aban IB, Wolfe GI, Cutter GR, et al. The MGTX experience: Challenges in planning and executing an international, multicenter clinical trial. *J Neuroimmunol* 2008;201-202:80-84.
3. Smith, G.C. Pell, J.P. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. *Br Med J* 2003;327:20-27.

Appendix

|           |             |                |                 |
|-----------|-------------|----------------|-----------------|
| Veral     | Bril        | Toronto        | Canada          |
| Marinos   | Dalakas     | Philadelphia   | PA              |
| Daniel    | Drachman    | Baltimore      | MD              |
| Raina     | Ernstoff    | Royal Oak      | MI              |
| Jonathan  | Goldstein   | New Haven      | CT              |
| Robert    | Griggs      | Rochester      | NY              |
| Charles   | Harper      | Rochester      | MN              |
| Reinhard  | Hohlfeld    | Munich         | Germany         |
| James     | Howard, Jr. | Chapel Hill    | NC              |
| Carlayne  | Jackson     | San Antonio    | TX              |
| Vern      | Juel        | Durham         | NC              |
| John      | Kissel      | Columbus       | OH              |
| Robert    | Leshner     | LaJolla        | CA              |
| Richard   | Lewis       | Detroit        | MI              |
| Robert    | Lisak       | Detroit        | MI              |
| Richard   | Mayer       | Baltimore      | MD              |
| Matthew   | Meriggioli  | Chicago        | IL              |
| Tahseen   | Mozaffar    | Chicago        | IL              |
| Michael   | Nicolle     | London         | Canada          |
| Joel      | Oger        | Vancouver      | Canada          |
| Lawrence  | Phillips II | Richmond       | VA              |
| Julie     | Rowin       | Chicago        | IL              |
| Lewis     | Rowland     | New York City  | NY              |
| Donald    | Sanders     | Durham         | NC              |
| Rup       | Tandan      | Burlington     | VT              |
| Steven    | Vernino     | Dallas         | TX              |
| David     | Weinberg    | Boston         | MA              |
| Allan     | Weiss       | St. Petersburg | FL              |
| Hans      | Katzberg    | Toronto        | Canada          |
| Katalin   | Scherer     | Tucson         | AZ              |
| Finn      | Somnier     | Copenhagen     | Denmark         |
| Nils Erik | Gilhus      | Bergen         | Norway          |
| Charlene  | Hafer-Macko | Baltimore      | MD              |
| David     | Locomis     | Pittsburgh     | PA              |
| Jan       | Verschuuren | Leiden         | The Netherlands |
| Janice    | Massey      | Durham         | NC              |
| Robert    | Pascuzzi    | Indianapolis   | IN              |