Appendix e-1. GDDI Subcommittee members

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-chair); Sonja Potrebic, MD, PhD (Co-Vice-Chair); Eric J. Ashman, MD, FAAN; Richard L. Barbano, MD, PhD, FAAN; Brian Callaghan, MD; Jane Chan, MD, FAAN; Diane Donley, MD; Richard M. Dubinsky, MD, MPH, FAAN; Terry Fife, MD, FAAN; Jeffrey Fletcher, MD; Michael Haboubi, MD; John J. Halperin, MD, FAAN; Yolanda Holler, MD; Andres M. Kanner, MD; Annette M. Langer-Gould, MD, PhD; Jason Lazarou, MD; Nicole Licking, DO; David Michelson, MD; Pushpa Narayanaswami, MBBS, DM, FAAN; Maryam Oskoui, MD; Richard Popwell, Jr., MD; Tamara Pringsheim, MD; Alejandro A. Rabinstein, MD, FAAN; Alexander Rae-Grant, MD; Anant Shenoy, MD; Kevin Sheth, MD, FAHA; Kelly Sullivan, PhD; Jonathan P. Hosey, MD, FAAN (Ex-Officio); Stephen Ashwal, MD, FAAN (Ex-Officio); Deborah Hirtz, MD, FAAN (Ex-Officio); Jacqueline French, MD, FAAN (AAN Guideline Historian, Ex-Officio, Voting)

Appendix e-2. Mission statement of GDDI

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-3. Evidence schemes for classifying articles

Therapeutic scheme

Class I
- Randomized, controlled clinical trial (RCT) in a representative population
- Masked or objective outcome assessment
- Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences
- Also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment
4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

Class II
- Cohort study meeting criteria a–e above or an RCT that lacks one or two criteria b–e
- All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences
- Masked or objective outcome assessment

Class III
- Controlled studies (including studies with external controls such as well-defined natural history controls)
- A description of major confounding differences between treatment groups that could affect outcome**
- Outcome assessment masked, objective, or performed by someone who is not a member of the treatment team

Class IV
- Did not include patients with the disease
- Did not include patients receiving different interventions

- Undefined or unaccepted interventions or outcome measures
- No measures of effectiveness or statistical precision presented or calculable

*Numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

Prognostic scheme

Class I

A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class II

A case-control study of a broad spectrum of persons with the condition compared to a broad spectrum of controls or a cohort study of a broad spectrum of persons at risk for the outcome (e.g. target disease, work status) where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class III

A case-control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data was collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

Class IV

Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

Appendix e-4: Classification of recommendations

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the confidence interval is > 2).