Practice Parameter: Neuroprotective Strategies and Alternative Therapies for Parkinson Disease (An Evidence-Based Review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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Abstract

Objective
To define key issues in the management of Parkinson disease (PD) relating to neuroprotective strategies and alternative treatments, and to make evidence-based treatment recommendations.

Methods
Two clinical questions were identified: 1) In a patient diagnosed with PD, are there any therapies that can slow disease progression? 2) Are there any nonstandard pharmacologic or nonpharmacologic therapies that have been shown to improve motor function in PD? Articles were classified according to a four-tiered level of evidence scheme. Recommendations were based on the evidence.

Results and Conclusions
1. Levodopa does not appear to accelerate disease progression. 2. No treatment has been shown to be neuroprotective. 3. There is no evidence that vitamin or food additives can improve motor function in PD. 4. Exercise may be helpful in improving motor function. 5. Speech therapy may be helpful in improving speech volume. 6. No manual therapy has been shown to be helpful in the treatment of motor symptoms, although studies in this area are limited. Further studies using a rigorous scientific method are needed to determine efficacy of alternative therapies.

Introduction

Statement of Purpose
The Quality Standards Subcommittee (QSS) develops scientifically sound, clinically relevant practice parameters to aid in the practice of neurology. This article addresses neuroprotective and alternative treatments for the

management of PD. These recommendations are meant to address the needs of specialists and nonspecialists caring for people with PD.

Background and Justification
PD is a neurodegenerative disorder characterized by the classic symptoms of bradykinesia, rigidity, and rest tremor. Although symptomatic therapy can provide benefit for many years, the disorder slowly progresses, eventually resulting in significant disability. Strategies to delay onset or slow progression of PD is an important consideration of overall treatment.

While the initiation of therapy has already been discussed in a previous Practice Parameter,[1] many nonstandard pharmacologic and nonpharmacologic therapies are currently employed by patients and caregivers. One study found that 63% of Patients with PD use nutritional supplements, but fewer than 50% of patients reported this use to their physicians;[2] only 4% were aware of possible drug supplement interactions.[3] Additional nonpharmacologic therapies such as acupuncture, food supplements, naturopathic, nutraceuticals, and physical, occupational, and speech therapies are also in common use.[4] This Practice Parameter is addressed to neurologists and all other clinicians who care for patients with PD.

Clinical Question Statement
This practice parameter addresses two clinically relevant questions regarding the management of PD:

1. Are there any therapies that can slow the progression of PD?
2. Are there any nonstandard pharmacologic or nonpharmacologic therapies that have been shown to improve motor function in PD?

Description of the Analytical Process

The QSS of the American Academy of Neurology identified five movement disorder specialists and a general neurologist with methodological expertise. For the literature review, the following databases were searched: MEDLINE, EMBASE, CINHAL, Cochrane Database of Systematic Reviews for the years 1997-2002. Only articles written in English were included. A second MEDLINE search covered 1966-August 2004, followed by a secondary search using the bibliographies of retrieved articles and knowledge from the expert panel extending to January 2005. The majority of articles were reviewed by the full panel. If a panelist was an author of one of the papers, at least two other panelists reviewed that paper. If a disagreement was identified, consensus was reached by discussion with the whole group. Conflicts of interest were disclosed. Support was provided by the American Academy of Neurology and writing meetings were funded by the Michael J. Fox Foundation. Panelists were not compensated.

For Question 1:
- Search terms: Parkinson disease, disease progression, antiparkinson agents, monoamine oxidase inhibitors, levodopa, amantadine, dopamine agonists, ascorbic acid, vitamin E, and coenzyme Q.
- The search produced 112 abstracts.
- Inclusion criteria: Studies of rates of disease progression in patients with early PD using potential neuroprotective agents. Articles dealing only with symptomatic benefit were excluded. At least 6 months of follow-up were required. Articles discussing selegiline were reviewed in a previous Practice Parameter. [1]
- Categories found: amantadine, coenzyme Q10, levodopa, pramipexole (with and without imaging), rasagiline, ropinirole (with imaging), thalamotomy, vitamin C, vitamin E.
- Results: Of the original 112 articles, 75 were excluded due to being off topic or review articles. Thirty seven articles were ordered and reviewed; 11 articles satisfied inclusion criteria.

For Question 2:
- Search terms: Parkinson disease, rehabilitation, complementary therapies, medicinal plants, vitamins, dietary supplements, homeopathy, holistic health, acupuncture, chiropractice, manipulation, physiotherapy, speech therapy, and tai chi.
- The search produced 167 abstracts.
- Inclusion criteria: At least 10 subjects included in study with treatment of at least 1 week duration. Categories found: naturopathic treatments, physiotherapy, speech therapy, vitamin therapy (folic acid, pyridoxine, ascorbic

acid, vitamin E, vitamin D, vitamin K 2), chiropractice, acupuncture, Alexander technique, music therapy, osteopathic manipulation.

– Results: Of the 167 articles, 51 were excluded as being off topic or review articles. A total of 116 articles were ordered and reviewed with 22 identified as satisfying inclusion criteria.

Analysis of the Evidence

Question 1:

Are there any therapies that can slow the progression of PD?

The ability to slow disease progression in PD is a major issue for clinicians and patients, and a major focus for research. Neuroprotection would delay decline of motor symptoms and preserve quality of life. However, a significant challenge exists in defining and measuring neuroprotection. The ideal method to demonstrate neuroprotection would be to identify a diminished rate of loss of these neurons. Currently, measurement of neurons can only be done postmortem, and even then, determining rate of decline poses a challenge. As direct visualization during the patient's life would be optimal, but is not possible at the present time, surrogate markers that are thought to reflect nigrostriatal neuron counts need to be employed.[5]

Potential clinical surrogate markers include ratings of motor impairment, general disability, quality of life measures, and time to a specific event such as delay for the initiation of symptomatic therapy, motor fluctuations, or death. However, as none of these have been validated, cautious interpretation of these studies is required.[6] Also, clinical surrogate measures may be confounded by the effects of symptomatic therapy.

Neuroimaging provides different surrogate markers. It can be used to assess the integrity of presynaptic dopaminergic neurons by assessing dopamine transporter sites, decarboxylase activity, and vesicular monoamine transport Type 2 sites.[6] Several types of neuroimaging markers have been used, including ^{18}F fluorodopa PET, which is primarily a measure of decarboxylase activity, and Beta-CIT, which measures dopamine transport. These methods are based on the assumption that there is a fixed relationship between decarboxylase activity and/or dopamine transporter (DAT) activity and the number of nigrostriatal neurons. However, that relationship may be perturbed by therapeutic intervention. It has been shown that neuroimaging surrogate measures may be confounded by the effects of pharmacologic intervention on tracer uptake independent of dopaminergic neuron changes.[7] Consequently, imaging may not accurately reflect the number of dopaminergic neurons. Thus, current evidence does not support the use of imaging as a surrogate endpoint in clinical trials.[6]

Another important factor is trial length. As the disorder progresses slowly, testing of a possible neuroprotective benefit and its permanence requires long-term follow-up over many years.

Eleven articles met the inclusion criteria for this question: seven Class I, one Class II, and three Class IV.

Vitamin E

Two articles were identified. The first [8] was a nonrandomized unblinded study without independent assessment which suggested a slower rate of progression in early Patients with PD treated with vitamin E (3200 IU/day) combined with vitamin C (3000 mg/day) (Class IV).[8] The second article was a randomized, blinded study with nearly complete outcome assessment, which examined time to initiation of levodopa therapy as the surrogate marker for neuroprotection (Class I).[9] A total of 800 patients were randomized to a dose of 2000 IU of vitamin E/day or placebo (with or without selegiline) and followed for 14 +/- 6 months. Primary endpoint was onset of disability requiring use of levodopa. Results showed no difference between the tocopherol and placebo groups in the average time to required levodopa (hazard ratio 0.91, 95% CI 0.74 to 1.12).

Riluzole

A single Class I, randomized, double blind, placebo controlled 6-month trial evaluated riluzole 50 mg BID compared to placebo with a primary outcome of change in Unified Parkinson's Disease Rating Scale (UPDRS).[10] No significant difference was found. However, the study was not sufficiently powered to exclude a modest neuroprotective benefit of riluzole.

Coenzyme Q10

One randomized, blinded Class I study (doses 300/600/1,200 mg/days) followed 80 patients for 16 months or until disability required levodopa.[11] The primary response variable was change in total UPDRS score. Subjects treated with CoQ10 had less disability as shown by a change in UPDRS from baseline (8 in controls and 6.4 in the 1,200mg group) ($p = 0.09$). Although the results did not reach statistical significance, they did meet the prespecified criteria for a positive trend. The study was designed to determine safety and tolerability in the dose range of 300 to 1,200 mg/day, and was underpowered to determine a neuroprotective benefit.

Levodopa vs. Placebo

A Class I, double-blinded, controlled trial randomized 361 Patients with PD to placebo or levodopa 150 mg/day, 300 mg/day, or 600 mg/day.[12] Primary outcome was masked assessment of change in UPDRS from baseline after 40 weeks of treatment and a 2-week washout. In addition, SPECT Beta-CIT was performed at baseline and week 40 in a subgroup of 116 patients. Patients randomized to all levodopa doses had significantly better UPDRS scores than patients on placebo, with the greatest improvement seen on the highest dose. Change in UPDRS on placebo was 7.8 (SD ± 9), at a dose of 150 mg levodopa was 1.9 (SD ± 6), at 300 mg 1.9 (SD ± 6.9), and at 600 mg -1.4 (SD ± 7.7). These results suggest that patients on a higher dose of levodopa had sustained functional improvement compared to their baseline even after a 2-week washout. However, it is possible that this washout period was not sufficient to exclude a persistent symptomatic effect. Patients on the highest dose of levodopa did develop more dyskinesias, but it is unclear whether this reflects a dose effect or disease progression. There was no significant difference in Beta-CIT uptake across the groups. In a post hoc analysis that included only patients with abnormal baseline Beta-CIT scans, patients on high dose levodopa had greater reduction on Beta-CIT uptake.

Pramipexole

A single Class I, randomized, controlled trial of 301 patients with early PD assessed treatment effects of levodopa vs pramipexole.[13] Eighty-two patients had a minimum of 12 hour washout permitting assessment of neuroprotective effect at 22, 32, and 46 months.[14] The primary outcome was change in UPDRS and change in Beta-CIT. At 46 months, there was no difference in the change from baseline in the UPDRS scores between the two treatment groups. At 46 months, a reduction of Beta-CIT uptake of 16 +/- 13.3 (pramipexole) vs 25.5 +/-14.1 in levodopa-treated patients ($p = 0.01$) was seen. However, many of the patients on pramipexole had concomitant levodopa treatment.

Ropinirole

One Class I pilot study examined 45 subjects in a prospective cohort treated with up to 1200 mg of levodopa and ropinirole up to 24 mg/day followed for 2 years and evaluated with fluorodopa PET, which revealed no difference between the two groups. Completion rate was 82%.[15]

One Class II single blind, prospective study included 162 patients eligible for analysis treated with ropinirole (up to 24 mg/day) or levodopa (up to 1,000 mg/day) for up to 24 months.[16] Both groups could also be supplemented with levodopa or with stable doses of amantadine or anticholinergics throughout the study. Completion rate was 63%. Endpoint was percent reduction in bilateral putamenal uptake of levodopa on fluorodopa PET. The reduction in the ropinirole group was 13.4% (SE 2.14) as compared to 20.3% (SE 2.35) in the levodopa group.

Rasagiline

In a single, Class I, randomized, double blind, 12 month study, 404 Patients with PD were randomized to rasagiline 1 mg/day, 2 mg/day, or placebo for 6 months followed by rasagiline 2 mg/day for 6 months.[17] A delayed start design for the trial was used due to the mild symptomatic benefit of rasagiline. Primary outcome was the change in total UPDRS from baseline at 12 months. Additional therapy was allowed with levodopa or dopamine agonists during the trial; the total amount of dopaminergic therapy in the two groups is not stated. Ninety-two percent of patients completed the study. Patients treated with rasagiline 2 mg/day had less of an increase in the mean adjusted UPDRS score compared to patients treated with placebo followed by rasagiline 2 mg/day (mean difference of 2.29 units). There was a -0.96 change in the activities of daily living (ADL) subsection in the UPDRS in the group taking rasagiline 2 mg for the whole year, as compared to the group initially taking placebo for six months followed by rasagiline 2 mg ($p = 0.005$). The results were felt to be compatible with a neuroprotective effect. However, it is possible that the difference in functional decline between the two groups was due to the added symptomatic benefit of rasagiline in the group treated for the full year.

Other Therapeis

We found one study each that assessed the potential of neuroprotective effectiveness of thalamotomy,[18] and amantadine.[19] Because of nonrandomized design and nonindependent outcome assessment, these studies were graded Class IV. We found no studies in early PD addressing the neuroprotective efficacy of creatine, glutathione, GDNF, minocycline, neuroimmunophillin, nonsteroidals, simple sugars (e.g. mannose), green tea, or stem cells.

We also reassesed the recommendation for selegiline from the previous Practice Parameter published in 2002[1], which stated that there was no evidence for a neuroprotective benefit for selegiline. No studies were identified that had been published after 2002 that would alter this conclusion.

Conclusion

Based on a sufficiently powered Class I study, we conclude that vitamin E probably does not delay the need for levodopa therapy. This reflects lack of neuroprotection.

Three single Class I studies using UPDRS as the outcome measure suggest there is no evidence of neuroprotection for riluzole, Coenzyme Q, or pramipexole (as compared to levodopa). However, the studies of riluzole and coenzyme Q were underpowered to rule out a possible benefit, particularly if modest.

Using neuroimaging as a surrogate marker for neuroprotection, there was a measurable decrease in striatal Beta-CIT uptake in patients randomized to levodopa vs. pramipexole. Based on one Class I and one Class II study, there was a measurable decrease in fluorodopa putaminal uptake in patients randomized to levodopa vs ropinirole. Given that these outcomes are not validated surrogate measures of neuroprotection and no placebo group was studied, the significance of these findings is uncertain.

In one Class I study, levodopa is possibly neuroprotective for at least 9 months and does not accelerate disease progression. The significance of the dyskinesias at the highest levodopa dose is unclear.

Early use of rasagiline, as compared to placebo, is associated with less deterioration in the UPDRS scores in a single Class I study. However, the additional symptomatic treatment (dopaminergic therapy) and possible symptomatic effect of rasagiline itself confounds the interpretation of whether this represents a neuroprotective effect.

Based on one Class IV study each, the benefit of thalamotomy or amantadine cannot be determined.

Recommendations

For patients with PD, treatment with 2,000 units of vitamin E should not be considered for neuroprotection (Level B).

There is insufficient evidence to support the or refute the use of riluzole (Level U), Coenzyme Q10 (Level U) pramipexole (Level U), ropinirole (Level U), rasagiline (Level U), amantadine (Level U), or thalamotomy (Level U) for neuroprotection.

Levodopa may be considered for initial treatment of PD (9 months) as it does not accelerate disease progression and is safe (Level B). There is no long term evidence to recommend levodopa for neuroprotection (Level U).

As reviewed in a previous Practice Parameter,[1] there is insufficient evidence to recommend the use of selegiline for neuroprotection (Level U).

Question 2:

Are there any nonstandard pharmacologic or nonpharmacologic therapies that have been shown to improve motor function in PD?

Use of complementary medication and treatment is common in Patients with PD; 40% of patients in the United States and 54% of patients in the United Kingdom use treatments such as herbs, vitamins, massage and acupuncture.[2, 20]

Food

Mucuna pruriens, also known as cowhage or velvet bean, has been recommended for treatment of PD by ancient Ayurvedic texts, and the seeds of *M pruriens* have been shown to contain levodopa. One small study of eight patients over a 4-hour observation period showed temporary motor benefit,[21] and two small open label studies suggested more prolonged benefit.[22, 23] Only one study was identified that fit the inclusion criteria, which enrolled 60 patients into an open label study for 12 weeks (Class IV).[24] Using UPDRS, a significant improvement was seen from baseline. Side effects were mild.

Vicia faba (broad or fava bean) has also been suggested to be therapeutic,[25, 26] as short term benefit can be seen in Patients with PD.[27] No articles fulfilled criteria for inclusion.

Vitamin Therapy

A number of vitamins may directly affect symptoms of PD, or affect levels of levodopa, potentially increasing or decreasing its effect.

Vitamin C can increase levels of levodopa, thereby prolonging benefit of action. One small study suggested improvement in the short term.[28] Folic acid[29] and folinic acid[30] have been shown to have no clinical benefit in small unblinded reports. No studies with any of these vitamins fulfilled criteria for review.

Vitamin E is widely used as a supplement, but has previously been shown to have no neuroprotective effect in PD (reviewed above).[9] This large, randomized placebo controlled trial with 800 patients also showed no clinical benefit (Class I).

Acupuncture

Acupuncture is one of the most frequently used treatment modalities in complementary medicine.[31] Several anecdotal and case reports suggest a symptomatic benefit to both motor and nonmotor symptoms.[32-34] One Class IV study of 20 patients suggested symptomatic benefit, although no objective improvement was demonstrated.[35]

Manual Therapy

A variety of manual therapy techniques including chiropractic manipulation,[36] osteopathic manipulation,[37] and Trager therapy[38] have all been suggested to be of benefit. The literature review did not reveal any studies that fulfilled the inclusion criteria, as the papers identified were either case reports or unblinded with small numbers.

One Class III study randomized 20 patients with PD to biofeedback therapy or placebo.[39] Study patients underwent a 15-week training period of biofeedback and relaxation. No differences were seen in motor function before and after therapy.

The Alexander technique (AT) requires developing awareness of posture in order to improve it.[40] A pilot study suggested benefit in PD.[41] In one Class III trial, with nonmasked outcome assessment, 58 Patients with PD were randomized to treatment with 24 AT sessions, 24 massage treatments, or no intervention for 12 weeks.[42] The primary outcome measure was a validated self assessment disability scale. Beck Depression Inventory and Attitude to Self Scale were also collected. The AT group showed significant improvement compared to the control group, with benefit maintained on the primary outcome at 6 months follow-up. The massage group revealed an improvement in some outcome measures.

Exercise Therapy

Exercise therapy (physical therapy) is sometimes used as an adjunct to pharmacological therapies in patients with PD.[43] Our literature review identified eight randomized trials comparing functional outcomes in patients with PD receiving exercise therapy to patients with PD receiving other therapies. Additionally we identified two systematic reviews of the same topic.[44, 45]

The physiotherapy interventions included: multidisciplinary rehabilitation including standard physical therapy and occupational therapy components[46]; “cued” exercises with visual (mirror), auditory (metronome), and tactile feedback[47]; treadmill training with body weight support[48, 49], balance training and high-intensity resistance training[50]; and active muscle therapy.[51] Some trials relied on techniques such as muscle stretch and reinforced

patterns of movement and active muscle contraction designed to facilitate proprioceptive neuromuscular function.[52, 53]

Outcome measures also varied and included the stand-walk-sit score[46]; falls during dynamic posturography testing[50]; ambulation speeds[49]; and various subscales of the UPDRS.[47] Follow-up duration ranged from 6 weeks to 8 months.

All studies randomized Patients with PD to the exercise therapy modality and the comparator, employed masked outcome assessments, and had near complete follow up. Four studies employed a cross-over design. Because none of the studies described concealed allocation techniques, all studies were graded Class II.

All of the studies resulted in improved functional outcomes which were significant in the variety of modalities used, including improved stand-sit-walk scores,[46] reductions in UPDRS ADL and motor subscores.[47] UPDRS bradykinesia scores,[51] increased ambulation speeds,[48, 49] and decreased falls during posturography.[50] Overall, however, the magnitude of the observed benefit was small. Additionally, the benefit was not sustained after exercise therapy was discontinued.

Speech Therapy

Patients with PD commonly develop dysarthria. Speech therapy is sometimes used to treat PD-related dysarthria. Our literature search strategy identified five randomized trials comparing functional outcomes in patients with PD receiving speech therapy. Additionally we identified two systematic reviews of the same topic.[54,55]

Two of the identified studies compared the effectiveness of one speech therapy modality to another.[56, 57] Three studies compared the effectiveness of speech therapy to no treatment.[58-60]

The speech therapies included individual therapy emphasizing prosodic features reinforced with[56, 58, 59] or without visual feedback[56]; therapy aimed solely at maximizing phonatory effort (Lee Silverman Voice Treatment)[57, 60]; and therapy aimed at increasing respiratory muscle activity.[57]

Outcome measures varied and included objective measures of speech volume [57, 59, 60]; a global assessment of speech quality—the Frenchay Dysarthria assessment[59]; and measures of prosodic intelligibility.[56] Study duration ranged from 1 month[59] to 48 months.[57]

Five studies employed assessors of outcome that were masked to treatment allocation [56, 57, 59] whereas one study used only objective, unmasked outcome measures.[60]

One study described concealed randomization,[56] whereas alternate allocation was employed in three studies.[57, 58, 60] One study did not describe allocation concealment.[59]

The number of patients with PD enrolled ranged from 12[59] to 45.[57] In the studies describing losses to follow-up, drop-out rates varied from 15%[56] to 18%[58] to 27%.[57]

Because of important differences in baseline characteristics after treatment allocation and unmasked, non-objective, non-independent outcome assessment we graded one study class IV.[58] Because of non-concealed treatment allocation or excessive losses to follow-up we graded three studies class II.[57, 59, 60] We classified one study Class I.[56]

In both studies comparing the efficacy of different speech therapy modalities,[56, 57] the authors did not statistically compare changes in outcomes from one therapy to another. Thus, it is impossible to determine if one modality was superior to another.

In the two class II studies comparing the effectiveness of speech therapy to no therapy, objective loudness of treated patients significantly improved by 11 dB[59] and 5.4 dB,[60] This improvement lessened but remained significant (3.5 dB) at 6 months.[60] These improvements are probably clinically important given that the average difference between objective speech loudness in patients with PD with dysarthria and healthy age-matched controls was 2.3 dB.[60]

Conclusions
Based on one Class IV study, the benefit of chronic use of *M pruriens* cannot be determined.

Vitamin E is probably ineffective for the treatment of PD. Vitamin C and folic acid have not been adequately studied to demonstrate effect on PD symptoms.

No controlled studies are available to demonstrate effectiveness of acupuncture. One uncontrolled study did not show motor benefit.

No studies were found that satisfied inclusion criteria for the evaluation of manual therapy (chiropractic, massage, osteopathic, Trager therapy). Biofeedback did not provide any benefit in one Class III study. Because there is only one Class III study, we conclude there is insufficient evidence to support or refute the use of the Alexander technique.

Based on eight Class II studies, various exercise modalities including multidisciplinary rehabilitation, active music therapy, treadmill training, balance training, and "cued" exercise training are probably effective in improving functional outcomes for

patients with PD. However, the functional improvement is small and not sustained.

Based on a single Class II study, individual speech therapy emphasizing prosodic features of pitch and volume with visual feedback is possibly effective in improving speech volume in patients with PD.

Based on a single Class II study, individual speech therapy aimed solely at maximizing phonatory effort is possibly effective in improving speech volume in patients with PD.

There is insufficient evidence to determine if any specific speech therapy modality is superior to another.

Recommendations
There is insufficient evidence to support or refute the use of *M pruriens* for the treatment of motor symptoms of PD (Level U).

For patients with PD, vitamin E (2,000 units) should not be considered for symptomatic treatment (Level B).

There is insufficient evidence to support or refute the use of acupuncture in PD (Level U).

There is insufficient evidence to support or refute manual therapy, biofeedback, or Alexander technique in the treatment of PD (Level U).

For patients with PD, exercise therapy may be considered to improve function (Level C). For patients with PD complicated by dysarthria, speech therapy may be considered to improve speech volume (Level C).

Recommendations for Future Research

The identification of neuroprotective agents to slow disease progression remains a major focus of research. A severe limitation in current studies has been the absence of accepted surrogate endpoints that mirror nigrostriatal dopaminergic neuron loss; reliable and validated surrogated endpoints need to be developed. Secondly, accurate early diagnosis and improved knowledge of disease progression will facilitate clinical trials of potential neuroprotective agents.

Another factor for consideration is that by the time of clinical diagnosis, over 70% of dopaminergic cell loss has already occurred. More emphasis needs to be placed on the development of methods to identify presymptomatic patients for clinical trials of potential neuroprotective therapies. Secondly, innovative trial designs with long term followup need to be implemented to provide convincing evidence of neuronal protection.

Alternative therapies are widely used by patients in PD treatment. Few studies are available to demonstrate safety or effectiveness of these treatments, exposing patients to the possibility of ineffective or possibly harmful treatments. These therapies need to be tested in the same rigorous manner as conventional therapies in order to provide an evidence-based rationale for their use.

Disclaimer

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Disclosure

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Appendix 1

Classification of Evidence for Therapeutic Articles

Class I

Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

1. primary outcome(s) is/are clearly defined
2. exclusion/inclusion criteria are clearly defined
3. adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias
4. relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II

Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above OR a RCT in a representative population that lacks one criterion a-d.

Class III

All other controlled trials including well-defined natural history controls or patients serving as own controls in a representative population, where outcome assessment is independently assessed or independently derived by objective outcome measurement.*

Class IV

Evidence from uncontrolled studies, case series, case reports, or expert opinion.

* 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).

Appendix 2

Classification of Recommendations

A = Established as effective, ineffective, or harmful 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 for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful 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 is unproven.

Appendix 3

Quality Standards Subcommittee Members

Jacqueline French, MD (Co-Chair); Charles E. Argoff, MD; Stephen Ashwal, MD (ex-officio); Christopher Bever, Jr., MD; John D. England, MD; Gary Franklin, MD, MPH (ex-officio); Gary H. Friday, MD; Larry B. Goldstein, MD; Deborah Hirtz, MD (ex-officio); Robert G. Holloway, MD, MPH; Donald J. Iverson, MD; Leslie Morrison, MD; Clifford J. Schostal, MD; David J. Thurman, MD, MPH; Samuel Wiebe, MD; William J. Weiner, MD, (facilitator).

Resources

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