Comprehensive systematic review summary: Treatment of cerebellar motor dysfunction and ataxia


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Abstract

Objective
To systematically review evidence regarding ataxia treatment.

Methods
A comprehensive systematic review was performed according to American Academy of Neurology methodology.

Conclusions
For patients with episodic ataxia type 2, 4-aminopyridine 15 mg/d probably reduces ataxia attack frequency over 3 months (1 Class I study). For patients with ataxia of mixed etiology, riluzole probably improves ataxia signs at 8 weeks (1 Class I study). For patients with Friedreich ataxia or spinocerebellar ataxia (SCA), riluzole probably improves ataxia signs at 12 months (1 Class I study). For patients with SCA type 3, valproic acid 1,200 mg/d possibly improves ataxia at 12 weeks. For patients with spinocerebellar degeneration, thyrotropin-releasing hormone possibly improves some ataxia signs over 10 to 14 days (1 Class II study). For patients with Friedreich ataxia, deferiprone possibly worsens ataxia signs over 6 months (1 Class II study). Data are insufficient to support or refute the use of numerous agents. For nonpharmacologic options, in patients with degenerative ataxias, 4-week inpatient rehabilitation probably improves ataxia and function (1 Class I study); transcranial magnetic stimulation possibly improves cerebellar motor signs at 21 days (1 Class II study). For patients with multiple sclerosis–associated ataxia, the addition of pressure splints possibly has no additional benefit compared with neuromuscular rehabilitation alone (1 Class II study). Data are insufficient to support or refute use of stochastic whole-body vibration therapy (1 Class III study).
The cerebellum is composed of the vermis, the hemispheres, and 3 cerebellar peduncles on each side, and contributes largely to balance and motor coordination. The causes of cerebellar dysfunction are numerous and include vitamin deficiencies, structural lesions (caused by tumors or trauma), infection, inflammation, toxins, neurodegeneration, genetics, stroke, multiple sclerosis (MS), and metabolic disorders. Motor signs resulting from cerebellar dysfunction may include some or all of the following: imbalance, impaired coordination, limb and body tremor, dysarthria, and oculomotor abnormalities. Other neurologic symptoms and signs may accompany cerebellar dysfunction, including dystonia, muscle weakness, oculomotor abnormalities, neuropathy, parkinsonism, spasticity, impaired visual acuity, and sensory impairment; these symptoms and signs are beyond the scope of this review. Mood, cognitive disorders, and autonomic dysfunction may also occur. Ataxia may result from cerebellar or sensory impairment.

There is currently no approved therapy to treat cerebellar motor dysfunction, and no pharmacologic or surgical treatment is routinely used. Various therapies have been studied in clinical trials for the past 40 years, although no consensus has been reached on their effectiveness. This comprehensive systematic review synthesizes the literature on the treatment of cerebellar motor dysfunction to answer the following questions:

1. For patients with cerebellar motor dysfunction, do pharmacologic therapies, compared with no (or alternative) treatments, improve motor symptoms with acceptable safety and tolerability?
2. For patients with cerebellar motor dysfunction, do surgical or other interventional therapies (e.g., physical training), compared with no (or alternative) treatments, improve motor symptoms with acceptable safety and tolerability?
3. For patients with cerebellar motor dysfunction, does transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), compared with no (or alternative) treatments, improve motor symptoms with acceptable safety and tolerability?

This article summarizes the systematic review findings and conclusions. Full text of the systematic review is available as a data supplement at http://npub.org/0t5ncn.

Description of the analytic process

This project used a hybrid of American Academy of Neurology (AAN) systematic review methodologic processes; the development panel used the AAN’s 2004 process manual1 for the overall approach but held a public comment period and applied the updated classification of evidence scheme for therapeutic studies that had been approved and then published as an amendment to the 2011 manual.2 A description of the exact methodology followed, including the convening of the author panel, literature search strategy, and the process for reviewing evidence, is available in the full-length review. Articles authored by individuals participating in the systematic review were assessed by nonconflicted panel members. Conflicts of interest were assessed and judged to be balanced when the comprehensive systematic review was initiated and again at its conclusion. Although new conflicts appeared during the multiyear process, at least half of the panel was without conflict throughout the entirety of the process. Studies without an independent control group are considered Class IV under the updated classification of evidence scheme. Because many studies predate the determination of genotypes causing cerebellar motor dysfunction, the development panel retained the nosology used by the authors of each article. As the pathophysiology and neurochemistry of the ataxias may vary between types, the different diagnoses were considered separately wherever possible. Adverse events are discussed in the full-length review.

Analysis of evidence

Question 1: For patients with cerebellar dysfunction, do pharmacologic therapies, compared with no (or alternative) treatments, improve motor symptoms with acceptable safety and tolerability?

Medications with evidence of benefit

4-Aminopyridine

Ten patients with familial episodic ataxia type 2 (EA2) were administered 4-aminopyridine 15 mg/d in a Class I randomized, double-blind, placebo-controlled, crossover study.3
After 3 months of treatment, the median monthly attack frequency was 1.65 (interquartile range 1.00–4.78) compared with a median monthly attack frequency of 6.50 (interquartile range 2.33–13.75) with placebo ($p = 0.03$).

4-Aminopyridine conclusion

For patients with EA2, 4-aminopyridine 15 mg/d probably reduces the frequency of ataxia attacks over a 3-month period (1 Class I study).

Riluzole

Forty patients with ataxia of mixed etiology were administered riluzole 100 mg/d in a randomized, double-blind, placebo-controlled, single-center Class I study. A 5-point decrease in International Cooperative Ataxia Rating Scale (ICARS) score after 4 weeks was seen in 9 of 19 patients receiving riluzole vs 1 of 19 patients receiving placebo (odds ratio [OR] 16.2, 95% confidence interval [CI] 1.8–147.1). Four more patients receiving riluzole experienced a benefit after 8 weeks (OR 39.0, 95% CI 4.2–364.2). Absolute risk difference was 63.2% (95% CI 33.5%–79.9%) after 8 weeks. Riluzole treatment resulted in greater mean decreases in the ICARS total and subscale scores compared with placebo (mean difference in ICARS total change −7.05 [95% CI −9.74 to −4.68]; subscales described in full-length review). Whether these changes reflect clinically meaningful changes is unknown. Because of the small number of participants with each condition and the varied signs and physiology of each condition, this study could not inform disease-specific conclusions.

A follow-up, randomized, double-blind, placebo-controlled, Class I study investigated the benefit of riluzole 50 mg twice daily for 12 months in 60 patients with spinocerebellar ataxia (SCA) or Friedreich ataxia (FA). The primary endpoint was the proportion of patients with an improved Scale for the Assessment and Rating of Ataxia (SARA) score at 12 months, which was better in the riluzole group (OR 8.00, 95% CI 1.95–32.83), including after a post hoc logistic regression analysis adjusting for sex, age, and ataxia type (OR 9.76, 95% CI 2.08–45.80), in the 55 patients who received treatment. Mean difference in change in SARA score was also better in the riluzole group (−1.50, 95% CI −2.59 to −0.40, at 3 months; −2.68, 95% CI −3.98 to −1.39, at 12 months).

Riluzole conclusion

For patients with ataxia of various etiologies, riluzole 100 mg/d is probably effective for short-term treatment as measured by the ICARS at 6 weeks (1 Class I study). In patients with SCA or FA, riluzole 100 mg/d is probably effective for improving ataxia as measured by the SARA at 12 months (1 Class I study). Patients receiving riluzole require monitoring of liver enzymes.

Weak evidence

Valproic acid

In a Class II, randomized, double-blind, placebo-controlled study, patients with SCA type 3 (SCA3)/Machado–Joseph disease were randomized to receive high-dose valproic acid (VPA) (1,200 mg/d), low-dose VPA (800 mg/d), or placebo for 12 weeks. Mean change in SARA total score over 12 weeks was significantly greater in the 1,200-mg/d group (−2.05) compared with both the 800-mg/d (−1.58) and placebo (−0.75) groups (analysis of variance $p = 0.021$). The clinical importance of this difference in mean change is uncertain.

VPA conclusion

For patients with SCA3, VPA 1,200 mg/d is possibly effective for improving SARA total score at 12 weeks (1 Class II study).

Thyrotropin-releasing hormone

A randomized, double-blind, placebo-controlled, Class II study (predating genetic testing) of 254 patients with “spinocerebellar degeneration” (SCD) administered 0.5 and 2 mg of thyrotropin-releasing hormone (TRH), intramuscularly, once daily for 2 weeks. A higher percentage of patients with late-onset cerebellar cortical atrophy and olivopontocerebellar atrophy were rated as “markedly improved” or “moderately improved” at 2 weeks when treated with TRH compared with placebo ($p < 0.05$, exact value not reported). In the overall group, more patients treated with TRH had a higher “improvement ratio” for the signs of dysarthria, standing, and gait disorder ($p < 0.05$, exact value not reported). The article focused only on signs that improved. The clinical significance of these change scores is unknown.

TRH conclusion

For patients with SCD, TRH use possibly improves some signs of ataxia over 10 to 14 days (1 Class II study). The clinical significance of these changes is uncertain.

Medications with evidence against benefit

Moderate evidence

Lithium carbonate

A double-blind, randomized, placebo-controlled, Class I study evaluated lithium carbonate (dosed to serum target levels of 0.5–0.8 mEq/L) in 62 patients with SCA3 who were ambulatory. After 48 weeks of treatment, no difference was seen in mean scores on the primary endpoint, the Neurological Examination Score for Spinocerebellar Ataxia (NESSCA), as assessed by a generalized estimation equation using baseline measurements as covariates (NESSCA total score −0.38 points in the lithium group vs placebo, 95% CI −1.7 to 1.0). No difference was observed on the SARA total score (a secondary outcome) at 48 weeks (lithium effect vs placebo −0.96, 95% CI −2.38 to 0.46). Small but statistically significant changes were noted in certain secondary outcome measures when those receiving lithium were compared with the placebo group; the clinical relevance of these scales is not established. In further analysis, the treatment group had less worsening on the cerebellar NESSCA (range: 0–7 points) at 24 weeks (−0.81, 95% CI −1.18 to −0.44) and 48 weeks (−0.64, 95% CI −1.05 to −0.23).

Lithium carbonate conclusion

For patients with SCA3 who are ambulatory, lithium probably does not improve ataxia over 48 weeks as measured by the
NESSCA and SARA total scores (1 Class I study), although minimal clinically important differences on these scales have not been established and small changes cannot be excluded.

**Weak evidence**

*Deferiprone*

A Class II study described the administration of deferiprone (20, 40, and 60 mg/kg/d divided in 2 doses) over 6 months to 72 patients with FA who were ambulatory. The 60-mg/kg/d group was discontinued because of perceived/observed worsening of ataxia. Patients receiving 40 mg/d experienced significant worsening of ataxia compared with the placebo group, as measured by the Friedreich Ataxia Rating Scale (FARS) total score (difference in mean change 5.4, 95% CI 1.5–9.3) and the ICARS total score (difference in mean change 4.7, 95% CI 0.5–8.9). There were no significant differences between the group treated with 20 mg/kg/d and the placebo group (difference in FARS total score mean change −0.3, 95% CI −3.8 to 3.2; difference in ICARS total score mean change −0.6, 95% CI −4.5 to 3.3).

*Deferiprone conclusion*

For patients with FA, deferiprone 40 mg/kg/d possibly worsens ataxia signs over 6 months (1 Class II study).

**Medications with conflicting results or insufficient evidence**

Pharmacologic therapies for which no conclusions for or against use could be drawn are described in the table, with details provided in the full-length review. The idebenone literature is described briefly here because this treatment has been the subject of 3 randomized controlled trials. In the first study, there was no difference in ICARS change scores at 6 months by analysis of covariance (p = 0.17), but the intermediate- and high-dose groups had a greater mean change on the ICARS compared with the placebo group (difference in change vs placebo: low-dose 5 mg/kg −1.99 [95% CI −7.54 to 3.57], Bonferroni-adjusted p = 1.00; intermediate-dose 15 mg/kg −6.24 [95% CI −10.89 to −1.60], Bonferroni-adjusted p = 0.03; high-dose 45 mg/kg −7.76 [95% CI −12.56 to −2.96], Bonferroni-adjusted p = 0.010); the difference in mean change on the FARS between the treatment and control groups was not significant, but the CIs included the possibility of clinically important effects. The second study found no difference in improvement on the ICARS scores between groups, but did not have sufficient precision to exclude a clinically important effect. A random-effects meta-analysis of these 2 studies showed a greater mean change on the ICARS in the idebenone group, but with CIs that included the possibility of no effect (difference in mean change −4.2, 95% CI −9.0 to 0.7, I² = 38%). When data for the 45-mg/kg group in the first study were combined with those for the 30- to 54-mg/kg group in the second study, the difference in mean score change between idebenone and placebo was −4.5 (95% CI −11.0 to 2.0, I² = 71%).

A third double-blind, placebo-controlled trial investigating idebenone for use in FA ended in 2010, but it could not be included, as it is unpublished and available data are insufficient for classification of evidence and analysis. According to a press release, there was no difference in the mean change in ICARS score from baseline between the active arms and placebo, and a meta-analysis of the manufacturer’s 3 studies showed no statistically significant mean change in ICARS scores between groups.

Because of these different findings, the lack of statistical precision, and the inability to incorporate a large unpublished randomized controlled trial, no conclusions could be drawn for or against idebenone use (table).

The manufacturer of idebenone is not currently pursuing approval of idebenone for the treatment of FA, and this medication is not routinely used for this indication in clinical practice. Idebenone is not approved for use within the United States.

**Question 2: For patients with cerebellar dysfunction, do surgical or other interventional therapies (e.g., physical training), compared with no (or alternative) treatments, improve motor symptoms with acceptable safety and tolerability?**

**Pressure splints**

A Class II study of patients with MS-associated ataxia randomized patients to receive neuromuscular rehabilitation only (control group, n = 13) or neuromuscular rehabilitation plus pressure splints (treatment group, n = 13) 3 times weekly for 4 weeks. No posttreatment differences were noted between groups for most gait parameters/equilibrium tests. Data were insufficient to calculate 95% CIs for between-group change scores.

*Pressure splints conclusion*

For patients with MS-associated ataxia, the addition of pressure splints to neuromuscular rehabilitation possibly has no additional benefit over neuromuscular rehabilitation alone (1 Class II study).

**Physical and occupational therapy**

Various therapy approaches have been evaluated to improve symptoms of ataxia; most studies in this area are rated Class IV. In a single Class I study, daily inpatient physical and occupational therapy for 4 weeks was compared with a wait-list control. At 4 weeks, patients with SCA type 6, SCA type 31, and idiopathic cerebellar ataxia receiving rehabilitation had a greater reduction in the SARA total score (mean difference −3.0, 95% CI −4.3 to −1.8) and a small but significant improvement in the Functional Independence Measure total score (mean difference 1.3, 95% CI 0.4–2.0).

*Physical and occupational therapy conclusion*

Four-week inpatient rehabilitation in patients with isolated degenerative ataxias probably improves ataxia and functional abilities as measured at 4 weeks (1 Class I study).
Stochastic vibration therapy

There is insufficient information to support or refute the use of stochastic whole-body vibration therapy in patients with SCAs (1 Class III study).16

Question 3: For patients with cerebellar dysfunction, does TMS or tDCS, compared with no (or alternative) treatments, improve motor symptoms with acceptable safety and tolerability?

A double-blind, Class II study compared 21 daily TMS treatments over the cerebellum with sham treatments in 74 patients with various ataxias.17 The patients treated with TMS had a greater reduction in timed 10-m walk (−1.1 seconds, estimated 95% CI −2.3 to −0.005) and 10-m steps (−1.7, estimated 95% CI −3.4 to −0.007), and a greater improvement in the number of tandem steps (1.0, estimated 95% CI 0.3−1.7) and standing capacity (as assessed on a 0- to 6-point scale with lower scores indicating better function (−0.32, estimated 95% CI −0.6 to −0.001). The clinical significance of these differences is uncertain.

A Class III, randomized, double-blind, crossover study18 compared a single session of anodal cerebellar tDCS with sham stimulation separated by at least 1 week in 19 patients with various ataxias. The SARA score was better after tDCS

### Table: Pharmacologic agents for which no conclusions can be drawn

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reference</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idebenone</td>
<td>Di Prospero 2007, Lynch 2010, MICONOS press release</td>
<td>For patients with FA, there is insufficient evidence to support or refute a change in ataxia with idebenone treatment (1 Class III study).</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Bier 2003, Mandelcorn 2004, Rice 1997</td>
<td>There is insufficient evidence to support or refute a benefit of ondansetron for treatment of cerebellar motor dysfunction because of conflicting Class III studies.</td>
</tr>
<tr>
<td>Dolasetron mesylate</td>
<td>Monaca-Charley 2003</td>
<td>There is insufficient evidence to support or refute a benefit of dolasetron mesylate for patients with a cerebellar syndrome secondary to MS (1 Class III study).</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Schulte 2001</td>
<td>There is insufficient evidence to support or refute a benefit of trimethoprim-sulfamethoxazole for patients with SCA3 (1 Class III study).</td>
</tr>
<tr>
<td>Zinc</td>
<td>Velazquez-Perez 2011</td>
<td>There is insufficient evidence to support or refute a benefit of zinc for patients with SCA2 (1 Class II study with limited precision).</td>
</tr>
<tr>
<td>L-Carnitine</td>
<td>Sorbi 2000</td>
<td>There is insufficient evidence to support or refute a benefit of L-carnitine for patients with degenerative cerebellar ataxia (1 Class III study).</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Kark 1981, Wessel 1997</td>
<td>There is insufficient evidence to support or refute a benefit of physostigmine for patients with cerebellar ataxia (2 Class III studies over different time periods and with limited descriptions of results).</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Botez 1996</td>
<td>There is insufficient evidence to support or refute a benefit of amantadine for patients with cerebellar ataxia (1 Class III study).</td>
</tr>
<tr>
<td>Branched-chain amino acids</td>
<td>Mori 2002</td>
<td>There is insufficient evidence to support or refute a benefit of branched-chain amino acids for patients with cerebellar ataxia (1 Class III study).</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>Zannolli 2012</td>
<td>There is insufficient evidence to support or refute a benefit of betamethasone for patients with ataxia-telangiectasia (1 Class III study).</td>
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</tbody>
</table>

Abbreviations: FA = Friedreich ataxia; MS = multiple sclerosis; RCT = randomized controlled trial; SARA = Scale for the Assessment and Rating of Ataxia; SCA2 = spinocerebellar ataxia type 2; SCA3 = spinocerebellar ataxia type 3.

The references cited here can be found in the full-length guideline, available online as a data supplement at http://npub.org/0t5ncn.
treatment vs sham (mean difference 1.40, 95% CI 0.94–1.85), as was the ICARS (mean difference 4.37, 95% CI 3.27–5.47).

Conclusion
TMS over the cerebellum possibly improves cerebellar motor function at 21 days in patients with SCD and olivoponto-cerebellar atrophy (1 Class II study). There is insufficient evidence to support or refute use of a single session of anodal cerebellar tDCS for the treatment of ataxia (1 Class III study).

Discussion and suggestions for future research
Although studies of populations with rare diseases are challenging, rigorous study design is critical to assess the outcomes associated with new therapeutic options. This is true for both pharmacologic and nonpharmacologic studies. In addition to the studies described here, numerous Class IV studies were identified in the literature search. Under the 2011 AAN process, as amended, masked pretreatment and post-treatment study designs are insufficient to achieve Class III status. Only 2 rehabilitation studies were identified with a classification better than Class IV, and yet in practice, many clinicians find it helpful to refer patients with ataxia for therapy to help with daily function if not the ataxia itself. This review focused specifically on treatment of cerebellar motor dysfunction and ataxia; many of these conditions have associated signs and symptoms both within and outside the neurologic system that could potentially benefit from therapies not covered in this review. Dietary changes, including the use of a gluten-free diet to treat ataxia, were outside the scope of this systematic review. In addition, historical treatment approaches, such as the use of acetazolamide for the treatment of EA2, can have clinical value even in the absence of clinical trial evidence.

Future research in cerebellar motor dysfunction should analyze and document specific causes (genotype); define groups of diseases according to their mechanism of action (e.g., gain vs loss of function, toxicity); and utilize more precise outcome measures, including clinical and functional rating scales. More specific and potent candidate drugs for both symptomatic and disease-modifying studies are needed, as well as more sensitive clinical measures and biomarkers. Moreover, long-term studies to detect disease-modifying potential beyond symptomatic treatment should be conducted. Finally, the clinical trials must be adequately powered to detect a meaningful difference for each etiology.

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Conflict of interest
The American Academy of Neurology (AAN) is committed to producing independent, critical, and truthful comprehensive systematic reviews (SRs). Significant efforts are made to minimize the potential for conflicts of interest to influence the conclusions of this SR. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the SRs and the developers of the SRs. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, systematic review projects. Drafts of the SR have been reviewed by at least 3 AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.1

Author contributions
Dr. Zesiewicz: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Wilmot: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Kuo: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Perlman: acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content. Dr. Greenstein: analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content.
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