AMERICAN ACADEMY OF NEUROLOGY®

Summary of Comprehensive Systematic Review for **Clinicians**

Treatment of Cerebellar Motor Dysfunction and Ataxia

This is a summary of the American Academy of Neurology (AAN) comprehensive systematic review, Treatment of Cerebellar Motor Dysfunction and Ataxia, which was published in *Neurology*® online on February 9, 2018, and appears in the March 6, 2018, print issue.

Please refer to the full comprehensive systematic review at *AAN.com/guidelines* for more information, including descriptions of the processes for classifying evidence and deriving conclusions.

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

Medications with evidence of benefit

Moderate evidence	For patients with episodic ataxia type 2, 15 mg/d of 4-aminopyridine probably reduces the frequency of ataxia attacks over a 3-month period (**1 Class I study**).
	For patients with ataxia of various etiologies, riluzole 100 mg/d is probably effective for short-term treatment as measured by the International Cooperative Ataxia Rating Scale (ICARS) at 8 weeks (**1 Class I study**). In patients with spinocerebellar ataxia (SCA) or Friedreich ataxia (FA), riluzole 100 mg/d is probably effective for improving ataxia as measured by the Scale for the Assessment and Rating of Ataxia (SARA) at 12 months (**1 Class I study analyzing a cohort combining patients with either SCA or FA; subgroup analyses not presented**). Patients receiving riluzole require monitoring of liver enzymes.
Weak evidence	For patients with SCA type 3 (SCA3), valproic acid, 1,200 mg/d is possibly effective for improving SARA total score at 12 weeks (**1 Class II study**). For patients with "spinocerebellar degeneration," thyrotropin-releasing hormone 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	For patients with SCA3 who are ambulatory, lithium probably does not improve ataxia over 48 weeks as measured by the Neurological Examination Score for Spinocerebellar Ataxia (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	For patients with FA, deferiprone 40 mg/kg/d possibly worsens ataxia signs over 6 months (**1 Class II study**).

Medications with conflicting results

Insufficient evidence	For patients with FA, there is insufficient evidence to support or refute a change in ataxia with idebenone treatment (**1 Class I study showed benefit at intermediate and high doses; 1 Class I study provided insufficient evidence to support or refute an effect; 1 RCT of unknown AAN class disclosed unpublished results showing no statistically significant change when treatment was compared with placebo**).
	There is insufficient evidence to support or refute a benefit of buspirone for treatment of cerebellar motor dysfunction (**conflicting Class III studies**).
	There is insufficient evidence to support or refute a benefit of L-tryptophan for treatment of cerebellar motor dysfunction (**conflicting Class III studies with limited available data**).
	There is insufficient evidence to support or refute a benefit of choline for treatment of ataxia (**conflicting Class III studies with limited available data**).

Clinical context

Without publication of the MICONOS trial completed in 2010, it is difficult to fully assess the impact of idebenone in patients with FA. From the available evidence, the AAN class of the MICONOS trial cannot be determined; moreover, it is also unknown whether the MICONOS trial and the associated meta-analysis are sufficient to conclude that idebenone has no benefit, or whether the 95% confidence intervals from these trials included the possibility of a clinically important effect. The manufacturer of idebenone is not currently pursuing approval or further study 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.

Medications with insufficient evidence

Insufficient evidence	For patients with SCA3, there is insufficient evidence to support or refute whether varenicline (mean dose of 1.67 mg/d) is effective in treating ataxia over 4 weeks, as measured by the SARA total score (**1 Class II study with insufficient precision for the primary outcome measure**).
	There is insufficient evidence to support or refute a benefit of ondansetron for patients with ataxia (**1 Class II study with insufficient precision, 1 Class III study with no statistics/insufficient precision, and 1 Class III cerebellar tremor study with only 2 assessable patients with cerebellar degeneration**).
	There is insufficient evidence to support or refute a benefit of dolasetron mesylate for patients with a cerebellar syndrome secondary to multiple sclerosis (MS) (**1 Class III study**).
	There is insufficient evidence to support or refute a benefit of trimethoprim-sulfamethoxazole for patients with SCA3 (**1 Class III study**).
	There is insufficient evidence to support or refute a benefit of zinc for patients with SCA type 2 (**1 Class II study with limited precision**).
	There is insufficient evidence to support or refute a benefit of L-acetylcarnitine for patients with degenerative cerebellar ataxia (**1 Class III study**).
	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**).
	There is insufficient evidence to support or refute a benefit of amantadine for patients with cerebellar ataxia (**1 Class III study**).
	There is insufficient evidence to support or refute a benefit of branched-chain amino acids for patients with cerebellar ataxia (**1 Class III study**).
	There is insufficient evidence to support or refute a benefit of betamethasone for patients with ataxia-telangiectasia (**1 Class III study**).

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?

Weak evidence	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**).
Moderate evidence	Four-week inpatient rehabilitation with physical and occupational therapy in patients with isolated degenerative ataxias probably improves ataxia and functional abilities as measured at 4 weeks (**1 Class I study**).
Insufficient evidence	There is insufficient information to support or refute the use of stochastic whole-body vibration therapy in patients with SCAs (**1 Class III study**).

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?

Weak evidence	TMS over the cerebellum possibly improves cerebellar motor function at 21 days in patients with spinocerebellar degeneration and olivopontocerebellar atrophy (**1 Class II study**).
Insufficient evidence	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**).

This comprehensive systematic review was endorsed by the A-TCP Children's Project.

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