Comprehensive systematic review: Treatment of cerebellar motor dysfunction and ataxia

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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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.

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T. Zesiewicz has served as a clinical advisor for Steminent Biotherapeutics; has received travel reimbursement from the Department of Neurology at University of Southern Florida; has received travel reimbursement for a Biohaven Pharmaceuticals meeting; has served on the editorial board for *Neurodegenerative Disease Management* and *Tremor and other Hyperkinetic Movements*; has a patent for Methods of Treating Disease-Induced Ataxia and Non-Ataxic Imbalance (US Patent No. 9463190 B2); and has received research support for her division for approximately 20 clinical trials for Parkinson disease (PD), Friedreich ataxia, and spinocerebellar ataxias (SCAs).

G. Wilmot has served on scientific advisory panels for Biohaven Pharmaceuticals and Santhera Pharmaceuticals, and has received financial or material research support or compensation from Friedreich's Ataxia Research Alliance, Reata Pharmaceuticals, and Shire.

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T. Ashizawa has nonfinancial competing interests with the Marigold Foundation, Myotonic Dystrophy Foundation, and the Muscular Dystrophy Association (MDA); receives honoraria from the NIH National Institute of Neurological Disorders and Stroke (NINDS) Neurological Sciences and Disorders B Study Section; received travel reimbursement from the MDA Medical Advisory Committee and the National Ataxia Foundation for the Ataxia Investigator Meeting; serves as an editor for PLoS ONE; has a patent (US Patent No. 6855497) on a DNA test for SCA type 10 (SCA10); receives funding for an NINDS research grant award R01NSNS083564; participates in a clinical trial of BHV-4157 (NCT02960893); and has received royalty payments from Baylor College of Medicine for a DNA test for SCA10 (US Patent No. 6855497).

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M. Armstrong serves on the Level of Evidence editorial board for *Neurology* (not compensated financially) and is an AAN evidence-based methodologist.

G. Gronseth serves as an associate editor (level of evidence review) for *Neurology*, serves on the editorial advisory board for *Neurology Now*, and is compensated by the AAN for methodologic activities.

K. Sullivan has received research support from the Georgia Governor's Office of Highway Safety and has a patent for Methods of Treating Disease-Induced Ataxia and Non-Ataxic Imbalance (US Patient No. 9463190 B2).

ABBREVIATIONS

4-AP: 4-aminopyridine
5-HT1A: 5-hydroxytryptamine subtype 1A
5-HT_3: 5-hydroxytryptamine subtype 3
AAN: American Academy of Neurology
AEs: adverse events
CCA: cerebellar cortical atrophy
EA2: Episodic ataxia type 2
FA: Friedreich ataxia
FARS: Friedreich's Ataxia Rating Scale
FIM: Functional Independence Measure
FXTAS: fragile X tremor ataxia syndrome
GAD: glutamic acid decarboxylase
ICARS: International Cooperative Ataxia Rating Scale
ILOCA: idiopathic late-onset cerebellar ataxia
MS: multiple sclerosis
MSA: multiple-system atrophy
MSA-C: multiple-system atrophy-cerebellar type
NESSCA: Neurological Examination Score for the Assessment of Spinocerebellar Ataxia
OPCA: olivopontocerebellar atrophy
OR: odds ratio
RCT: randomized controlled trial
SARA: Scale for the Assessment and Rating of Ataxia
SCA: spinocerebellar ataxia
SCA1: spinocerebellar ataxia type 1
SCA2: spinocerebellar ataxia type 2
SCA3: spinocerebellar ataxia type 3
SCA28: spinocerebellar ataxia type 28
SCD: spinocerebellar degeneration
tDCS: transcranial direct current stimulation
TMS: transcranial magnetic stimulation
TRH: thyrotropin-releasing hormone
VPA: valproic acid

ABSTRACT
Objective: To systematically review evidence regarding ataxia treatment.
Methods: A comprehensive systematic review was performed according to AAN 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 (FA) or spinocerebellar ataxia (SCA), riluzole probably improves ataxia signs at 12 months (1 Class I study). For patients with SCA type 3 (SCA3), 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 10–14 days (1 Class II study). For patients with SCA3 who are ambulatory, lithium probably does not improve signs of ataxia over 48 weeks (1 Class I study). For patients with FA, 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) treatment, 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) treatment, 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) treatment, improve motor symptoms with acceptable safety and tolerability?

This comprehensive systematic review focuses on treatment of cerebellar motor dysfunction (cerebellar ataxia), which often constitutes symptomatic management. Management of other elements of the included diseases, such as ataxia resulting from sensory changes, other neurologic disturbance (e.g., parkinsonism), mood changes, and extraneurologic manifestations, are not included in this review.

DESCRIPTION OF THE ANALYTIC PROCESS

The American Academy of Neurology (AAN) Guideline Development, Dissemination, and Implementation Subcommittee (appendices e-1 and e-2) invited neurologists and scientists with expertise in ataxia and methodology to perform this comprehensive systematic review. 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. No panelist of the systematic review was permitted to rate or assess his or her own work; articles authored by individuals participating in the systematic review were assessed by nonconflicted panel members.

The project used a hybrid systematic review methodology, using the AAN's 2004 process manual[e1] for the overall approach, but the updated classification of evidence scheme for therapeutic studies that was already approved and later published as an amendment to the 2011 manual.[e2] There was also a public comment period for a near-final draft, a process described in the 2011 manual.[e2] The MEDLINE and EMBASE databases were searched from 1966 to June 2012. An updated pragmatic literature search of MEDLINE was performed on September 22, 2016, to capture studies published after 2012. Appendix e-3 lists the key words and phrases used in the search. Because tremor is a sign of several disease processes, it was not specifically included in the search strategy; however, if it was assessed as an outcome in studies of ataxia treatment, tremor results were reviewed. Central vestibular dysfunction, which may accompany some cerebellar disorders, was not specifically included in the search strategy.

The searches identified 9,195 articles pertaining to the treatment of motor signs of cerebellar dysfunction. The titles and abstracts of these articles were reviewed by at least 2 panel members. Complete articles were reviewed if they were controlled trials, observational studies, cohort studies, or open-label studies. Studies without an independent control group receiving a different intervention were not further reviewed once identified, as they are considered Class IV under the updated classification of evidence scheme. Articles were also excluded if they examined only basic science, diagnostic methods, or phenotypic descriptions, or if motor signs of cerebellar dysfunction were not an outcome measure. The panel selected 369 articles for full-text review, which were then reviewed for relevancy and, if appropriate, rated by at least 2 panelists working independently of each other using the AAN criteria for therapeutic classification (appendix e-4). Panel members did not rate their own research. A summary classification table including formally rated Class IV articles is available at Neurology.org (appendix e-5). Articles that were rated Class IV were not further considered; 32 studies rated Class III or higher were included in the final review (appendix e-6). When drawing conclusions, panelists considered not only whether results were statistically significant, but also whether the 95% CIs included or excluded potentially clinically important differences. In circumstances where study results were not statistically significant, only those studies with CIs precluding the possibility of a clinically important benefit resulted in conclusions of lack of benefit or of harm. Results are presented as strong, moderate, or weak according to the number and class of available studies, as stipulated by the 2004 AAN methodology.[e1] The draft systematic review was posted for 30-day public comment ending September 12, 2016; 11 individuals provided feedback. A table of responses to comments is available upon request.

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. The term *olivopontocerebellar atrophy* or *OPCA* was coined by Dejerine and Thomas in 1900 on the basis of neuropathologic presentation, and referred to patients with sporadic adult-onset progressive cerebellar ataxia.[e3] However, the term *OPCA* defined a cerebellar-plus syndrome encompassing several neurodegenerative syndromes, including multiple-system atrophy (MSA), autosomal dominant ataxia, and spastic paraplegia.[e4] Because the term *OPCA* referred to a variety of

neurodegenerative diseases that included ataxia and is not thought to represent a single neurologic entity, the development panel has described the phenomenology of patients whose diagnoses used this term in the literature review described here.

Clinical rating scales are commonly used to assess ataxia severity and are often used as the endpoint of clinical trials for ataxia. Frequently used scales include the International Cooperative Ataxia Rating Scale (ICARS), Scale for the Assessment and Rating of Ataxia (SARA), and Friedreich's Ataxia Rating Scale (FARS). These scales assess clinical features of ataxia, including gait, balance, speech, and limb movement through various tasks. Generally, these scales provide subscale scores for a specific sign or focus and a total score to quantify overall ataxia sign severity.

ANALYSIS OF EVIDENCE

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

Medications with evidence of benefit

Strong evidence

No pharmacologic therapies had strong evidence of benefit in patients with cerebellar motor dysfunction.

Moderate evidence

4-aminopyridine

Episodic ataxia type 2 (EA2) is an autosomal dominant disorder characterized by distinct episodes of ataxia, vertigo, dysarthria, and progressive cerebellar atrophy, and is caused by mutations of the calcium channel gene *CACNA1A* on chromosome 19p13.10.[e5] Aminopyridines have been hypothesized as potential therapeutic agents in patients with ataxia owing to their antagonistic effect on potassium channels and potential enhancement of axonal conduction.[e6,e7] Ten patients with familial EA2 were administered 4-aminopyridine (4-AP) 15 mg/d in a randomized, double-blind, placebo-controlled, crossover study (1 Class I study).[e8] 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 ($p = 0.03$). Adverse events (AEs) included nausea (2 patients given 4-AP, 1 patient given placebo), epigastric discomfort (2 patients given 4-AP), and palpitations (1 patient given 4-AP); no AEs led to treatment discontinuation.

Conclusion

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

Riluzole

Although the exact mechanism of action of riluzole is unknown, experts have hypothesized that this medication increases the uptake of glutamate by cerebellar astrocytes in several ataxia types in order to ameliorate damage caused by excitotoxicity, which lends support to riluzole use as a potential therapy for cerebellar ataxia.[e9] Other possible mechanisms of action include riluzole's

effect on sodium and potassium channels.[e10–e13] Forty patients with ataxia of mixed etiology (fragile X tremor ataxia syndrome [FXTAS]; Friedreich's ataxia [FA]; spinocerebellar ataxia type 1 [SCA1], SCA type 2 [SCA2], and SCA type 28 [SCA28]; MS; MSA-cerebellar type [MSA-C]; anti-glutamic acid decarboxylase [GAD] and anti-Yo cerebellar ataxia) were administered riluzole 100 mg/d in a randomized, double-blind, placebo-controlled single-center Class I study.[e14] Among the patients on riluzole, a 5-point drop in ICARS after 4 weeks was seen in 47.4% (9 of 19 participants) vs 5.3% (1 of 19 participants) in placebo group (odds ratio [OR] = 16.2, 95% CI 1.8–147.1). After 8 weeks, this difference became greater: 68.4% (13/19) vs 5.3% (1/19) (OR = 39.0, 95% CI 4.2–364.2). Absolute risk difference was 63.2% (95% CI 33.5%–79.9%) after 8 weeks. Treatment with riluzole for 8 weeks resulted in greater mean decreases in the ICARS total and subscale scores compared with placebo in the combined population (mean difference in ICARS total change -7.05 [95% CI -9.74 to -4.68]; mean difference in static function change -2.79 [95% CI -4.30 to -1.28], mean difference in kinetic function change -4.48 [95% CI -6.09 to -2.87], mean difference in dysarthria change -0.79 [95% CI -1.20 to -0.38]). Whether these changes reflect clinically meaningful changes is unknown. The largest clinical improvement (ICARS decrease) among patients taking riluzole was noted in patients with FXTAS (n = 1, 12-point improvement), anti-GAD antibodies (n = 1, 12-point improvement), SCA1 (n = 2, 9.5-point improvement), anti-Yo cerebellar ataxia (n = 1, 10-point improvement), and MSA-C (n = 3, 8-point improvement). Patients with ataxia syndromes of unknown origin (n = 5) improved 1.6 points, and patients with FA (n = 3) improved 3 points. Those with MS (n = 2) and SCA28 (n = 2) were only in the placebo group. Because of the small number of participants with each condition and the varied signs and physiology of each condition, this study cannot inform treatment of specific diseases. Two patients experienced an increase in alanine aminotransferase, and one patient experienced transient vertigo during treatment.

A follow-up randomized, double-blind, placebo-controlled Class I study investigated the benefit of riluzole 50 mg BID for 12 months in 60 patients with SCA or FA.[e15] The primary endpoint was the proportion of patients with an improved 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). Two patients in the riluzole group had an increase in liver enzymes (less than 2 times above normal limits) that did not require treatment withdrawal.

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 8 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

Valproic acid (VPA) acts via various mechanisms, including by inhibiting certain histone deacetylase isoforms. Via this mechanism, VPA is hypothesized to have neuroprotective and

anti-inflammatory properties. In a Class II randomized, double-blind, placebo-controlled study,[e16] patients with SCA3/Machado–Joseph disease (MJD) were randomized to receive high-dose VPA (1,200 mg/d), low-dose VPA (800 mg/d), or placebo for 12 weeks. The study included 12 patients who had previously participated in a single-dose VPA tolerance study. 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 (ANOVA $p = 0.021$). The clinical importance of this difference in mean change (1,200 mg/d vs 800 mg/d = -0.47, 1,200 mg/d vs placebo = -1.3, 800 mg/d vs placebo = -0.83) is uncertain. The only subscale for which the ANOVA analysis showed a statistically significant difference in mean change between groups was for stance ($p = 0.009$); the mean change in this subscale was greater in the 1,200-mg/d group (-0.83) than in the 800-mg/d (-0.17) and placebo (-0.25) groups. The most frequent AEs in the VPA group were dizziness (36%), loss of appetite (32%), and abdominal distension (23%). VPA may also cause tremor and parkinsonism (CNS Drugs 2016).[e17,e18]

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
Thyrotropin-releasing hormone (TRH) has been hypothesized as a treatment for ataxia because of its effects on noradrenaline metabolism in the cerebellum and brainstem. A randomized, double-blind, placebo-controlled Class II study of 254 patients with "spinocerebellar degeneration" (SCD) administered 0.5 and 2 mg of TRH, intramuscularly, once daily for 2 weeks.[e19] This study predates genetic testing. The primary outcome was a 14-grade visual analog scale. A higher percentage of patients with late-onset cerebellar cortical atrophy and OPCA—ataxias thought to be more cerebellar than spinocerebellar—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. AEs were reported in 50% of patients taking TRH 2 mg, 38% of patients taking TRH 0.5 mg, and 21% of patients taking placebo. The most common AEs fit in the category of gastrointestinal symptoms (38% of patients taking 2 mg, 42% of patients taking 0.5 mg, and 3% of patients taking placebo), cardiovascular (19% of patients taking 2 mg, 17% of patients taking 0.5 mg, and 12% of patients taking placebo), and "psychoneurologic" (19% of patients taking 2 mg, 6% of patients taking 0.5 mg, and 11% of patients taking placebo). One patient experienced a decrease in the white blood cell count (severity not reported).

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

Medications with evidence against benefit
Strong evidence
No pharmacologic therapies had strong evidence against benefit in patients with ataxia.

Moderate evidence

Lithium carbonate

Lithium carbonate is hypothesized to be a treatment for cerebellar motor dysfunction owing to reports of inhibition of glycogen synthase kinase-3β in preclinical models of Huntington's disease, SCA1 and SCA3.[e20] 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.[e20] After 48 weeks of treatment, no difference was seen in mean scores on the primary endpoint, the Neurological Examination Score for the Assessment of 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 measure) 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 (word speed-PATA rate 0.37, 95% CI 0.14–0.73; Spinocerebellar Ataxia Functional Index 0.32, 95% CI 0.10–0.54; and Composite Cerebellar Functional Score -0.03, 95% CI -0.05 to -0.003); the clinical relevance of these scales is not established. In further analysis,[e21] 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). There was no difference in progression on the SARA subscales between groups. AE type and severity were reportedly similar between groups, but supplementary tables detailing AEs were not accessible.

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

Deferiprone is an orally administered iron chelator, hypothesized to target mitochondrial dysfunction and altered iron metabolism that occurs in patients with FA.[e22] 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.[e22] The 60 mg/kg/d group was discontinued because of perceived/observed worsening of ataxia. Additional withdrawals among patients receiving active treatment included serum ferritin decrease (n = 2) and neutropenia (n = 1). Patients receiving 40 mg/d experienced significant worsening of ataxia compared with the placebo group, as measured by the 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). Cardiac outcomes were also evaluated but are outside the scope of this review.

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

Idebenone

Idebenone is an antioxidant and has been hypothesized to be a treatment for FA targeting oxidative stress and impaired cellular energy production that result from reduced frataxin expression. Two Class I studies evaluated idebenone for the treatment of ataxia in patients with FA. In the study randomizing 48 patients to 1 of 4 treatment arms (5 mg/kg, 15 mg/kg, 45 mg/kg, and placebo), there was no difference in ICARS change scores at 6 months by ANCOVA analysis ($p = 0.17$), 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 $p = 0.010$), with the Jonckheere trend test showing dose-dependent improvement on the ICARS ($p = 0.03$).[e23] The publication describes no difference in change from baseline on the FARS after 6 months of idebenone treatment ($p = 0.47$), including when assessing for dose-dependent trends ($p = 0.14$). However, when using the figure for the full cohort to calculate the difference in mean score changes on the FARS between the treatment and control groups, the CIs for each dose included the possibility of clinically important effects (low dose 0.8, 95% CI -13.2 to 14.8; intermediate dose -2.2, 95% CI -15.9 to 11.6; high dose -3.5, 95% CI -17.3 to 10.3). A prespecified analysis of patients with ICARS scores of 10–54 (patients who were not wheelchair bound) showed improvement in ICARS scores ($p = 0.01$) but not in FARS scores ($p = 0.31$) by ANCOVA.[e23] The AE frequency was similar in each group. One pediatric patient receiving the high dose developed neutropenia after 6 months, leading to treatment discontinuation.

The second study randomized 70 patients with FA and baseline ICARS scores of 10–54 to either 450 or 900 mg/d of idebenone (in those with a body weight ≤ or > 45 kg, respectively, corresponding to 10–20 mg/kg; n = 22), 1,350 or 2,250 mg/d of idebenone (corresponding to 30-54 mg/kg; n = 24), or placebo (n = 24).[e24] Although this study concluded that there was no difference in improvement on the ICARS scores between groups, analysis of the figures suggests that the study did not have sufficient precision to exclude a clinically important effect (mean difference in score change on the ICARS when comparing intermediate-dose idebenone to placebo -1.2, 95% CI -7.4 to 5.0; high-dose vs placebo -1.1, 95% CI -6.2 to 4.0). The same was true in assessment of figures for the FARS, a secondary endpoint measure (mean difference in change on the FARS when intermediate-dose idebenone was compared with placebo -2.1, 95% CI -9.2 to 5.0; high-dose idebenone compared with placebo -1.8, 95% CI -7.7 to 4.0). Patients receiving high-dose treatment were more likely to experience gastrointestinal tract irritations (n = 14) than those receiving low-dose treatment (n = 7) or placebo (n=10).

To address the limited precision with the second study, the guideline panel performed a random-effects meta-analyses of ICARS change scores between baseline and 6 months, combining similar doses. When the 15-mg/kg group in the first study was combined with the 10- to 20-mg/kg group of the second study, the random-effects meta-analysis showed a greater mean change in the idebenone group, but with CIs that include the possibility of no effect (difference

in mean change -4.2, 95% CI -9.0 to 0.7, I^2 = 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 treatment vs placebo was -4.5 (95% CI -11.0 to 2.0, I^2 = 71%). Results were similar when comparisons used only patients with ICARS scores of 10–54 from the first study (data not shown; mean change scores calculated from figures).

A third double-blind, placebo-controlled trial investigating idebenone for use in FA was identified. The MICONOS study[e25] studied 3 idebenone doses (low-dose 180 mg or 360 mg, depending on body weight; mid-dose 450 mg or 900 mg; and high-dose 1,350 or 2,250 mg) over 12 months in 232 patients with FA of all ages and disease severity. The study was completed in 2010; however, no related publication was identified, nor were results reported via clinicaltrials.gov. The study cannot be classified on the basis of available evidence. According to a press release,[e26] there was no difference in the primary outcome (mean change in ICARS score from baseline) between the active arms and placebo. The press release also stated that a meta-analysis of the manufacturer's 3 studies showed no statistically significant mean change in ICARS score between high-dose idebenone and placebo groups, or between combined mid- and high-dose groups and placebo. This meta-analysis could not be repeated for this systematic review because MICONOS study results were unavailable.

Conclusion

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).

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% CIs 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.

Buspirone

The serotonergic system's role in regulating motor output has motivated the investigation of buspirone, a serotonin 5-hydroxytryptamine subtype 1A (5-HT1A) receptor agonist, to treat ataxia. Two Class III studies investigating buspirone use in ataxia were identified. One randomized placebo-controlled Class III study evaluated buspirone 1 mg/kg for 4 months in patients with cerebellar cortical atrophy (CCA) and reported a 32% improvement in kinetic score (p = 0.04) and time standing with feet together (p = 0.006) (methodology and detailed data not reported).[e27,e28] Buspirone, 30 mg twice per day, was evaluated over a 2-week period in a Class III double-blind, randomized, placebo-controlled, crossover study of 20 patients with ataxia,

including SCA1, SCA2, SCA3, SCA type 6 (SCA6), SCA type 17; FA; dentatorubral-pallidoluysian atrophy, and idiopathic.[e29] No difference in ICARS score was observed in a comparison of mean posttreatment scores between the buspirone and placebo arms (-1.74, 95% CI -6.24 to 2.76). Dizziness and drowsiness were experienced by approximately 10% of patients.

Conclusion
There is insufficient evidence to support or refute a benefit of buspirone for treatment of cerebellar motor dysfunction (conflicting Class III studies).

L-Tryptophan
L-tryptophan has been hypothesized to alter cerebellar motor function through its serotonergic effects. Two Class III studies investigated the use of L-tryptophan for the treatment of cerebellar motor dysfunction. In the first study, L-tryptophan was evaluated in 30 patients with ataxia due to a variety of causes (inherited and acquired, including infarctions, MS, FA, and cerebellar atrophy). The total daily dose was not specified, and treatment was administered in a double-blind fashion for 4 months. Statistical improvements in timed walk, speech, and writing were noted in patients receiving L-tryptophan (estimated difference in timed walk with L-tryptophan -2.6 sec, 95% CI -4.9 to -0.3 sec; estimated difference in time to pronounce an arbitrary phrase with L-tryptophan 0.4 sec, 95% CI -0.7 to -0.1 sec; and estimated difference time to write name with L-tryptophan -2.0, 95% CI -3.2 to -0.8). The clinical significance of these differences is uncertain. No differences were observed between groups on other measures, including rapid alternating movements and standing tasks. No patients dropped out of the study, and there were no important AEs observed.[e30] The second study evaluated hydroxytryptophan up to 1,000 mg/d for 10 months in patients with FA, OPCA, and cerebellar atrophy. No effects on cerebellar signs were noted (data not reported). Eight patients reported minor gastrointestinal AEs.[e31]

Conclusion
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).

Choline
A deficiency of brain acetylcholine has been proposed in patients with various ataxia types, suggesting that choline, the precursor to acetylcholine, might provide symptomatic benefit. Four Class III placebo-controlled crossover studies evaluated various choline doses in patients with various types of cerebellar degeneration, predating genetic testing.

The first study enrolled 6 inpatients with "marked chronic cerebellar ataxia" and included 4-day treatment arms where patients received either 5 g of choline/d (divided QID) or placebo.[e32] Outcome measures included the Purdue pegboard score, spiral drawing, handwriting, and clinician assessments of finger–nose and heel–shin testing and gait, including a turn where each patient's performance was ranked from 1 to 12. No statistically significant differences were identified; insufficient details were provided to calculate CIs.

The second study enrolled 11 patients with cerebellar degeneration and 5 with spinocerebellar degeneration.[e33] Patients were randomized to receive either 3 g of choline/d for 3 weeks followed by 6 g of choline/d for 3 weeks, or matching placebo, with each treatment arm lasting 6 weeks.

The outcome measure was the "mean dot distance" from the 2-mm target. There was no significant difference between treatment arms (estimated posttreatment difference -0.61 mm when choline treatment at 6 weeks was compared with placebo, 95% CI -1.67 to 0.46). The clinical relevance of this outcome measure is uncertain.

In the third study, 14 patients with "predominantly cerebellar disability" from a variety of sources were randomized to two 6-week treatment arms separated by a 1-week washout, where patients received either choline (4 g/d for 3 weeks followed by 150 mg/kg/d for 3 weeks) or placebo.[e34] Of the 13 patients receiving active drug, 1 improved on multiple assessments, and 12 reported no functional improvement. Limited outcomes were reported.

In the final study, 20 patients with ataxia (7 with FA, 7 with mixed spinocerebellar ataxia, and 6 with primary cerebellar degeneration) were randomized to 6-week treatment arms consisting either of placebo or choline, with choline treatment consisting of either 6 g/d (divided QID) or 12 g/d (divided QID) dosing.[e35] Fourteen patients alternated between placebo and 1 of the 2 choline doses, and 6 patients alternated between the 2 choline doses. Ataxia signs were rated on a 0- to 5-point scale, where 0 indicated normal function and 5 indicated the task was impossible owing to ataxia. Change scores were recorded as no change, improvement, or worsening. A functional disability questionnaire was also administered. Four of 6 patients with primary cerebellar degeneration, 3 of 7 patients with mixed ataxia, and 3 of 7 patients with FA showed "definite degrees of improvement" while taking choline, although statistical comparisons between groups were not performed.

AEs in these studies included dose-dependent nausea, abdominal discomfort, diarrhea, and headaches.

Conclusion
There is insufficient evidence to support or refute a benefit of choline for treatment of ataxia (conflicting Class III studies with limited available data).

Medications with insufficient evidence
Varenicline
Varenicline is a partial agonist at α4β2 neuronal nicotinic acetylcholine receptors and is indicated for smoking cessation. This medication has been evaluated in one controlled Class II study of 20 patients with genetically confirmed SCA3.[e36] After a 4-week stable dosing period, a mean dose of 1.67 mg/d had no impact on the SARA total score (effect size 0.40, 95% CI -0.02 to 0.82), although CIs were broad and included the possibility of important and unimportant effects. Findings were similar for SARA subscale scores. After correction for multiple comparisons, only rapid alternating movements (effect size 0.32, 95% CI 0.11–0.53) remained statistically significant. The other 2 SARA subscale items described as statistically significant (gait effect size 0.55 [95% CI 0.03–1.08] and stance effect size -0.61 [95% CI -1.16 to -0.06]) were no longer significant after correction for multiple comparisons. The same was true for outcome measures other than the SARA scores. AEs were mild and included nausea in 30% of patients, vivid dreaming in 7% of patients, and leg tingling in 2% of patients.

Conclusion

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).

Ondansetron

One Class II and 2 Class III studies evaluated the use of ondansetron, a serotonin 5-hydroxytryptamine subtype 3 (5-HT_3) receptor antagonist, in patients with ataxia. In a Class II study of 46 patients with CCA, MSA, FA, familial cerebellar degeneration, and other disorders, ondansetron 8 mg twice a day for 1 week was compared with placebo.[e37] No difference was seen in the posttreatment ICARS scores between groups (ondansetron: 37.5 ± 19.4, placebo 36.4 ± 14.1; mean difference with ondansetron 1.1, 95% CI -8.8 to 11.0), but the 95% CI included potentially clinically important benefit and harm.

A Class III crossover study evaluated 4 patients with ataxia after traumatic brain injury. Patients underwent a 1-week baseline assessment and a 1-week single-blind placebo assessment, and then, for each of the subsequent 3 weeks were randomized to receive ondansetron 4 mg TID, ondansetron 8 mg TID, or placebo TID in 1-week blocks. The 5 outcome measures were a self-assessment rating, measures of upper limb ataxia, measures of lower limb ataxia, measures of truncal ataxia, and the Functional Independence Measure (FIM). When the 5 areas of testing were considered, the greatest combined improvement was seen in the area of lower limb ataxia, where patients improved 10.4% vs baseline during the 4-mg arm, and 10.7% vs baseline during the 8-mg arm.[e38] No statistical analyses were performed because of the small sample size; thus, this study had limited ability to contribute to conclusions. AEs in these studies were mild and included constipation, headache, and dystonia.

A second Class III crossover study compared a single 8-mg intravenous dose of ondansetron with placebo in 20 patients with "moderate to severe cerebellar tremor" from MS (n = 16), familial cerebellar degeneration (n = 3), and residual ataxia from lithium toxicity (n = 1).[e39] Patients received a single injection and were evaluated within 90 minutes of treatment; the alternate agent was administered similarly approximately 1 week later. The primary outcome measure was rater-judged change in spiral copying between pretreatment and posttreatment (approximately 60 minutes later), where the blinded evaluator rated the change as "no difference apparent," "mild improvement," or "moderate/marked improvement." One patient with cerebellar degeneration was not tested because of the severity of her symptoms. Spiral copying was "superior" in 13 of 19 patients after receiving ondansetron, compared with only 1 of 19 with placebo ($p < 0.001$ using a 2-tailed McNemar test). The nine-hole peg test was a secondary outcome measure, but 8 patients could not perform this test because of tremor severity. Of patients completing the test, the mean time for completion was 79 seconds after treatment with ondansetron and 86 seconds after treatment with placebo ($p = 0.08$ using a Wilcoxon rank sum 2-tailed test for paired data). Of the 20 patients, 12 perceived superior tremor control with ondansetron and 8 noticed no difference between treatment arms; none identified placebo as superior ($p = 0.01$ using a 2-tailed McNemar test). Because only 2 assessable patients had cerebellar degeneration, however, generalizability cannot be determined.

Conclusion

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).

Dolasetron mesylate
One Class III single-dose crossover study of dolasetron mesylate (a 5-HT_3 receptor antagonist) studied 34 patients with a cerebellar syndrome secondary to MS. Patients with MS who had either a relapsing-remitting (n = 10) or secondary progressive (n = 24) form of the disease and who presented with a cerebellar syndrome and a Kurtzke score greater than 2 were randomized to receive a single 100-mg IV dose of dolasetron mesylate or placebo.[e40] There was a 1-week washout period between study arms. After correction for multiple comparisons, no statistically significant between-group differences were observed on any outcome measure. Data were insufficient for calculation of CIs. No AEs were reported.

Conclusion
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).

Trimethoprim-sulfamethoxazole
Trimethoprim-sulfamethoxazole has been hypothesized to improve spasticity and increase biopterin and homovanillic acid levels, which have been reported to be reduced in patients with SCA3. A Class III crossover study evaluated trimethoprim-sulfamethoxazole (combination of trimethoprim 160 mg and sulfamethoxazole 800 mg, twice daily for 2 weeks, followed by a combination of trimethoprim 80 mg and sulfamethoxazole 400 mg, twice daily for 5.5 months) in 22 patients with SCA3.[e41] The two 6-month treatment arms were separated by a 4-week washout period. On a modified ataxia rating scale (where higher scores indicate worse performance), mean 6-month scores were mildly worse in the treatment group (mean difference 0.8, estimated 95% CIs -3.3 to 4.9), but the 95% CI included potentially clinically important changes favoring both trimethoprim-sulfamethoxazole and placebo. Two patients dropped out: one because of rash while taking placebo and one because of a suicide attempt while on active drug. Other AEs included minor gastrointestinal symptoms.

Conclusion
There is insufficient evidence to support or refute a benefit of trimethoprim-sulfamethoxazole for patients with SCA3 (1 Class III study).

Zinc
In a Class II randomized, double-blind, placebo-controlled trial, 36 Cuban patients with SCA2 were randomized to receive zinc 50 mg/d or placebo for 6 months.[e42] Both groups had a reduction in SARA score over the 6 months of the study, with no difference in mean change in SARA total scores or subscores (numbers not provided). When end-of-study SARA scores were estimated from a figure, no difference was seen in SARA scores after 6 months of treatment (mean difference in zinc group vs placebo -1.25, 95% CI -4.75 to 2.25). The 95% CI included potentially clinically important changes favoring both zinc and placebo. AEs were considered mild, and only 2 were considered treatment related (details not reported).

Conclusion
There is insufficient evidence to support or refute a benefit of zinc for patients with SCA2 (1 Class II study with limited precision).

L-acetylcarnitine
L-acetylcarnitine acts on oxidative metabolism and has been hypothesized to improve signs of cerebellar motor dysfunction in patients with degenerative ataxias. One Class III crossover study evaluated the use of L-acetylcarnitine 2,000 mg/d vs placebo in 6-month treatment arms. Thirty patients with degenerative cerebellar ataxias were enrolled: 11 with FA, 10 with idiopathic late-onset cerebellar ataxia (ILOCA), and 3 with an SCA type (1 with SCA1 and 2 with SCA2).[e43] Only 24 patients completed the study and were analyzed (dropouts included 1 patient with FA who died of cardiac rupture, 1 with ILOCA with a fractured hip after a fall, and 4 who dropped out for nonmedical reasons; treatment arm and purported relation of AEs to treatment are not stated). Otherwise, no AEs (including changes in heart rate, blood pressure, or laboratory results) were reported in either treatment group. Patients with FA and those with ILOCA were analyzed as separate groups, but analyses were primarily within-group analyses rather than comparisons of treatment and placebo arms.

Conclusion
There is insufficient evidence to support or refute a benefit of L-acetylcarnitine for patients with degenerative cerebellar ataxia (1 Class III study).

Physostigmine
Two Class III studies examined the effect of the cholinergic alkaloid physostigmine on ataxia. In the first study,[e44] patients with FA, OPCA, progressive peroneal atrophy with ataxia, combined atrophy of the cerebral and cerebellar cortices, "ragged-red ataxia," sensory neuropathy with cerebellar atrophy, ataxia-telangiectasia, adolescent-onset arylsulfatase deficiency, and Ramsay-Hunt syndrome received either physostigmine salicylate 1 mg orally (starting at 3 mg/d and increasing to 8 mg/d) or placebo in 3-month blocks. Some patients received treatment in a random fashion, and others were randomized to a triple crossover with 2 treatment and 2 placebo phases. The outcomes were physician-graded rating of ataxia, with each task graded on a 0–5 scale and assessed via video. Twenty-eight patients provided informed consent, but 7 were excluded owing to loss of videotape (n = 1) or use of a random rather than triple-crossover pattern. Of the remaining 21, the study considered 13 to be responders and 8 to be nonresponders, with the effect of physostigmine reported to be significantly better than placebo ($p < 0.025$), but with little detailed outcome information provided.

In the second study, 8 patients with idiopathic cerebellar ataxia and 11 patients with autosomal dominant cerebellar ataxia received either physostigmine administered via a patch (6 mg/24 hours) or placebo for 4 weeks.[e45] A lack of clinical or statistical change in the overall group was reported (clinical score improved an average of 0.63 with placebo and 1.84 with treatment, *p* value not reported). Eight patients improved more or deteriorated less with placebo, and 7 patients improved more or deteriorated less with physostigmine.

AEs of oral treatment included nausea in 1 patient; treatment administered via patch was associated with mild itching and rash at the patch site, minor headache, and diarrhea.

Conclusion
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).

Amantadine
Amantadine, an antiviral and antiparkinsonian agent, at doses of 200 mg/d was evaluated for 3 to 5 months in 36 patients with OPCA and 27 patients with phenotypic FA in a randomized, double-blind, placebo-controlled study (Class III).[e46] Blinded assessors indicated that 15/29 patients receiving amantadine had improvement in upper extremity function vs only 1/28 with placebo ($p < 0.001$); when OPCA and FA groups were analyzed separately, improvement was noted in both groups with amantadine vs placebo ($p < 0.05$ in FA and $p < 0.001$ in OPCA). Six participants with OPCA dropped out (3 were noncompliant on placebo, 1 due to gastrointestinal AEs on placebo, 1 with weight loss on active treatment, and 1 with a severe sleep disorder on active treatment) as did 1 participant with FA (due to a severe sleep disorder while receiving active treatment).

Conclusion
There is insufficient evidence to support or refute a benefit of amantadine for patients with cerebellar ataxia (1 Class III study).

Branched-chain amino acids
Branched-chain amino acids are proposed to stimulate intracellular glutamate metabolism. One Class III crossover study evaluated the use of branched-chain amino acids (1.5, 3.0, or 6.0 mg daily) vs placebo in the treatment of 16 patients with ataxia (SCA6 [8], OPCA [5], SCA type 7 [1], and CCA [10]).[e47] At 4 weeks, a significant decrease in ICARS scores occurred with branched-chain amino acid use when the 3.0-mg daily dose was compared with placebo (mean difference -2.89, 95% CI -5.3 to -0.5), but the differences for the 1.5-mg and 6.0-mg doses were not significant (data insufficient to calculate CIs). No AEs were reported.

Conclusion
There is insufficient evidence to support or refute a benefit of branched-chain amino acids for patients with cerebellar ataxia (1 Class III study).

Betamethasone
Steroids have been reported to improve cases of ataxia-telangiectasia in case reports and case series.[e48,e49] A Class III double-blind crossover study evaluated betamethasone 0.1 mg/kg/d for 30 days in 13 children with ataxia-telangiectasia (1 Class III study) and symptomatic ataxia. The median difference in the change in ICARS score was 13 points better in the treatment arm (-13, 95% CI -19 to -5.5), with betamethasone treatment also resulting in statistically greater improvements in the posture/gait subscale (median -5, 95% CI -9.5 to -1.5) and kinetic subscale (median -8, 95% CI -10 to -0.5). One patient receiving active treatment discontinued the study because of asthenia that occurred during dose tapering. Other AEs included increased body mass

index, cholesterol and high-density lipoprotein cholesterol, and decreased blood phosphorus, none of which led to treatment discontinuation.[e50]

Conclusion
There is insufficient evidence to support or refute a benefit of betamethasone for patients with ataxia-telangiectasia (1 Class III study).

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.[e51] Although both groups improved on a number of measures using pre- and posttreatment comparisons, no posttreatment differences were noted between treatment groups for most gait parameters or equilibrium tests. Data were insufficient to calculate 95% CIs for between-group change scores. No difference in posttreatment Expanded Disability Status Scale scores was noted between groups (-0.3 in treatment vs control group, 95% CI -0.6 to 0.04).

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. In a single Class I study, daily inpatient physical and occupational therapy for 4 weeks was compared with a 4-week wait list in a randomized controlled clinical trial enrolling 42 patients with isolated cerebellar ataxia caused by degenerative cerebellar diseases. The SARA and FIM were the primary outcomes. The study was rated Class I for 4-week outcomes; functional status was also described at 12 and 24 weeks, but these data are considered Class IV, as there was no control group (after 4 weeks, the control group also received the intervention such that there was no control group at 12 and 24 weeks).[e52] Patients with SCA6 (n = 20), SCA type 31 (n = 6), and idiopathic cerebellar ataxia (n = 16) were included. At 4 weeks, patients 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 FIM total score (mean difference 1.3, 95% CI 0.4–2.0). Other outcomes were also significantly improved in the treatment group.

Conclusion
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).

Stochastic vibration therapy

Stochastic whole-body vibration therapy was used in 32 patients with SCA1, SCA2, SCA3 and SCA6 in 1 Class III study.[e53] Vibration treatment consisted of 5 episodes of 60 seconds of stimulation at 6.5 Hz followed by 60 seconds of rest. A sham group followed the same procedure but only received 1 Hz of stimulation. After 4 treatments over 8 days, the day 8 SARA total score improved -1.3 points in the treatment group (95% CI -2.8 to 0.08) and -0.6 in the control group (95% CI -1.8 to 0.5), but the control group had lower SARA total scores at baseline, and no between-group differences were calculated. There was no significant difference in posttreatment scores between the 2 groups (-2.0, 95% -5.6 to 1.7), but CIs could not exclude the possibility of a meaningful effect.

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

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 sporadic and hereditary cerebellar degeneration (including SCA6) and OPCA.[e54] The patients treated with TMS had a greater reduction in timed 10-m walk (-1.1 sec, estimated 95% CI -2.3 to -0.005) and 10-m steps (-1.7, estimated 95% CI -3.4 to -0.007), a greater improvement in the number of tandem steps (1.0, estimated 95% CI 0.3–1.7), and a greater improvement in standing capacities 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 study[e55] compared a single session of anodal cerebellar tDCS with sham stimulation separated by at least 1 week in 19 patients with ataxia (relating to SCA1, SCA2, SCA type 38, FA, ataxia with oculomotor apraxia type 2, MSA-C, FXTAS, or an idiopathic process). The SARA score was better after tDCS 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 OPCA (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

This comprehensive systematic review identified a paucity of studies investigating the treatment of cerebellar motor dysfunction despite recent advances in the understanding of pathogenicity and genetic contributions. 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 posttreatment study designs are insufficient to achieve Class III status.[e2] 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. No studies of acetazolamide in EA2 identified for this review achieved higher than a Class IV evidence rating.

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.

DISCLAIMER

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CONFLICT OF INTEREST STATEMENT

The American Academy of Neurology 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 three 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.[e1]

Appendix e-1. AAN GDDI mission

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-2. AAN GDDI members 2015–2017

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD; (Co-Vice-Chair); Eric J. Ashman, MD; Stephen Ashwal, MD; Brian Callaghan, MD; Jane Chan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Jeffrey Fletcher, MD; Gary S. Gronseth, MD (Senior Evidence-based Medicine Methodology Expert); Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; David Michelson, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Jacqueline French, MD (Guideline Process Historian)

Appendix e-3. Complete search strategy

((((((ataxia*) OR "spinocerebellar ataxia" OR "spinocerebellar ataxias" OR "spinocerebellar degeneration" OR "spinocerebellar degenerations" OR “spinocerebellar atrophy”) OR SCA) OR "idiopathic late onset cerebellar ataxia") OR iloka) OR “machado-joseph”) AND ((treatment*) OR acetazolamide) OR amantadine) OR aminopyridine) OR "branched chain amino acid") OR buspirone) OR carnitine) OR choline) OR cronassial) OR cycloserine) OR dexamphetamine) OR dopamine) OR fluoxetine) OR gabapentin) OR hydroxytryptophan) OR "insulin like growth factor") OR "intravenous immunoglobulin") OR lamotrigine) OR levodopa) OR lisuride) OR "local anesthetic") OR memantine) OR mexiletine) OR ondansetron) OR physostigmine) OR pregabalin) OR rapamycin) OR sulfamethoxazole) OR "sulfamethoxazole trimethoprim") OR taltirelin) OR tandospirone) OR tetrahydrobiopterin) OR "thyrotropin-releasing hormone") OR "trimethoprim-sulphamethoxazole") OR varenicline) OR vigabatrin) OR zinc sulphate) OR zolpidem) OR "botulinum toxin") OR "deep brain stimulation") OR "fetal tissue graft") OR "umbilical cord") OR "occupational therapy") OR "physical training") OR "physical therapy") OR "psychological rehabilitation") OR "thalamic stimulation") OR "transcranial magnetic stimulation") OR "branched chain amino acids") OR "fetal tissue grafts") OR “voluntary postural control”) OR “fatty acid”) OR lecithin)

Medline Search strategy October 2015

((((((ataxia*) OR "spinocerebellar ataxia" OR "spinocerebellar ataxias" OR "spinocerebellar degeneration" OR "spinocerebellar degenerations" OR “spinocerebellar atrophy”) OR SCA) OR "idiopathic late onset cerebellar ataxia") ~~OR iloka)~~ OR “machado-joseph”) AND ((treatment*) OR acetazolamide) OR amantadine) OR aminopyridine) OR "branched chain amino acid") OR buspirone) OR carnitine) OR choline) OR cronassial) OR cycloserine) OR dexamphetamine) OR dopamine) OR fluoxetine) OR gabapentin) OR hydroxytryptophan) OR "insulin like growth factor") OR "intravenous immunoglobulin") OR lamotrigine) OR levodopa) OR lisuride) OR "local anesthetic") OR memantine) OR mexiletine) OR ondansetron) OR physostigmine) OR pregabalin) OR rapamycin) OR sulfamethoxazole) OR "sulfamethoxazole trimethoprim") OR taltirelin) OR tandospirone) OR tetrahydrobiopterin) OR "thyrotropin-releasing hormone") OR "trimethoprim-sulphamethoxazole") OR varenicline) OR vigabatrin) OR zinc sulphate) OR zolpidem) OR "botulinum toxin") OR "deep brain stimulation") OR "fetal tissue graft") OR "umbilical cord") OR "occupational therapy") OR "physical training") OR "physical therapy") OR "psychological rehabilitation") OR "thalamic stimulation") OR "transcranial magnetic stimulation") OR "branched chain amino acids") OR "fetal tissue grafts") OR “voluntary postural control”) OR “fatty acid”) OR lecithin)

Appendix e-4. AAN rules for classification of evidence for risk of bias

Therapeutic scheme

Class I

A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:

a. concealed allocation

b. no more than 2 primary outcomes specified

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*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

ii. 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).

iii. 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.

iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.

f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate

Class II

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.) All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including studies with external controls such as well-defined natural history controls). (Alternatively, a crossover trial missing both of the following 2 criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.) A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV
Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.
*Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any 1 of the 3 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).

Appendix e-5. Summary classification table

Intervention	Reference (first author, y)	Study class	Rationale for class (if not Class I)
Question 1			
3,4-DAP	Strupp, 2011[e8]	Class I	N/A
3,4-DAP	Tsunemi, 2010[e56]	Class IV	No control group
Riluzole	Ristori, 2010[e14]	Class I	N/A
Riluzole	Romano, 2015[e15]	Class I	NA
Idebenone	Di Prospero, 2007[e23]	Class I	N/A
Idebenone	Lynch, 2010[e24]	Class I	N/A
Idebenone	Hausse, 2002[e57]	Class IV	No control group
Idebenone	Artuch, 2002[e58]	Class IV	No control group
Idebenone	Pineda, 2008[e59]	Class IV	No control group
TRH	Sobue, 1983[e19]	Class II	No primary outcome measure, no allocation concealment
TRH	Kimura, 1983[e60]	Class IV	No control group
TRH	Yoshida, 1986[e61]	Class IV	No control group
Deferiprone	Pandolfo, 2014[e62]	Class II	No information on randomization methods/allocation concealment; >20% dropout if considering the cohort that was discontinued, follow-up numbers differ between text and diagram; accept safety as single primary outcome
Lithium carbonate	Saute, 2014[e20]; Saute, 2015[e21]	Class I	N/A
Buspirone	Lou, 1995[e63]	Class IV	No control group
Buspirone	Trouillas, 1996[e27]	Class III	No description of potential important confounding baseline characteristics between groups; no allocation concealment, no primary outcome
Buspirone	Assadi, 2007[e29]	Class III	Lack of comparison of baseline characteristics for treatment-order groups
Tryptophan	Trouillas, 1988[e30]	Class III	No information on randomization process, no allocation concealment, no primary outcome measure, no information on baseline differences between groups

Tryptophan	Wessel, 1995[e30]	Class III	No allocation concealment, no primary outcome, no information on baseline differences between treatment-order groups
Tryptophan	Currier, 1995[e64]	Class IV	No control group
Choline	Sehestad, 1980[e33]	Class III	No primary outcome, no allocation concealment, no baseline comparison of treatment-order groups
Choline	Austin, 1984[e33]	Class III	No primary outcome, no allocation concealment, many baseline characteristics not compared
Choline	Lawrence, 1980[e34]	Class III	No allocation concealment, no primary outcome, no information on baseline differences between treatment-order groups
Choline	Livingstone, 1981[e35]	Class III	No primary outcome, no allocation concealment, no information on baseline characteristics between treatment-order groups (only baseline ataxia scores)
Varenicline	Zesiewicz, 2012[e36]	Class II	>20% dropout
Ondansetron	Bier, 2003[e37]	Class II	Lack of allocation concealment
Ondansetron	Mandelcorn, 2004[e38]	Class III	No allocation concealment, no primary outcome, no information on baseline differences between treatment-order groups
Ondansetron	Rice, 1997[e39]	Class III	No information on randomization process, no allocation concealment, no information on baseline differences between treatment-order groups
Dolasetron mesylate	Monaca-Charley, 2003[e40]	Class III	No primary outcome, no information on baseline differences between treatment-order groups
Trimethoprim-sulfamethoxazole	Schulte, 2001[e41]	Class III	No information on randomization process, no allocation concealment, multiple primary outcome measures, no information on baseline differences between treatment-order groups
Zinc	Valezques-Perez, 2011[e42]	Class II	No allocation concealment, no primary outcome; cannot interpret subscales because there is no information on baseline differences in subscales

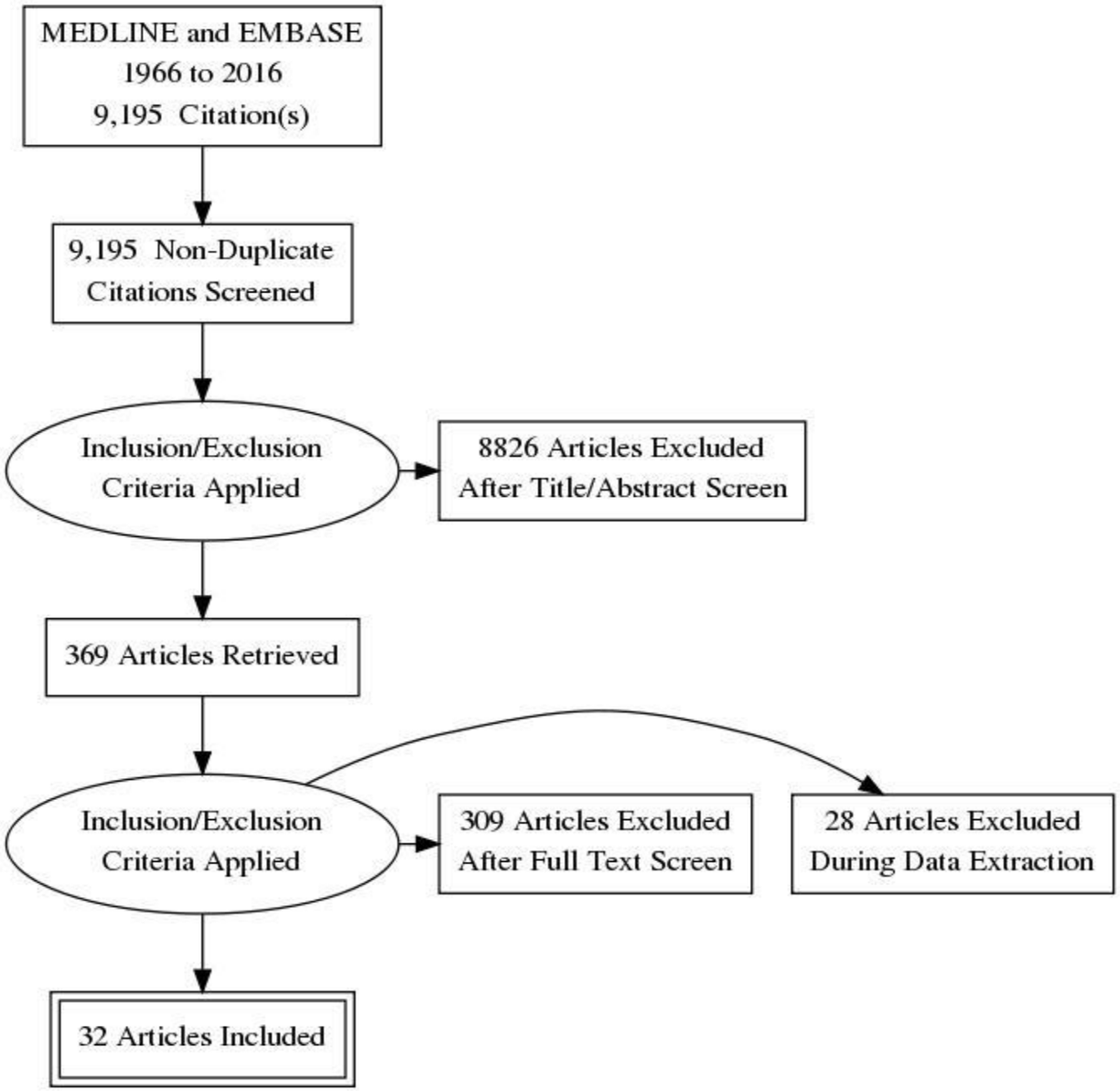
L-carnitine	Sorbi, 2000[e43]	Class II	No primary outcome, no allocation concealment, no baseline comparison of treatment-order groups
Physostigmine	Kark, 1981[e44]	Class III	No information on randomization process/allocation concealment, no primary outcome measure, no information on baseline differences between treatment-order groups, less than 80% included in analysis
Physostigmine	Wessel, 1997[e45]	Class III	No allocation concealment, no description of baseline differences between treatment-order groups
Amantadine	Botez, 1996[e46]	Class III	No allocation concealment, high dropout, no ITT, no description of potential important confounding baseline characteristics between groups (there are descriptions of FA vs OPCA but not placebo vs treatment; baseline scores provided but not potential confounders)
Branched-chain amino acids	Mori, 2002[e47]	Class III	Lack of comparison of baseline characteristics for treatment-order groups
Betamethasone	Zannolli, 2012[e50]	Class III	No information on baseline differences between treatment-order groups
Betamethasone	Broccoletti, 2011[e48]	Class IV	No control group
Betamethasone	Broccoletti, 2008[e49]	Class IV	No control group
Acetazolamide	Yabe, 2001[e65]	Class IV	No control group
Erythropoietin	Boesch, 2008[e66]	Class IV	No control group
Acetyl-dl-leucine	Bremova, 2015[e67]	Class IV	No control group
Immunotherapy	Jones, 2015[e68]	Class IV	No control group
Immunotherapy	Nanri, 2016[e69]	Class IV	No control group
Nicotinamide	Libri, 2014[e70]	Class IV	No control group
Interferon-gamma	Wells, 2015[e71]	Class IV	Review describing only Class IV data (no control group)
Valproic acid	Lei, 2016[e72]	Class II	Lack of allocation concealment; assume SARA total score was primary outcome; some baseline differences (e.g., age, disease duration) that were not accounted for but judged to be mild
Question 2			

Pressure splints	Armultu, 2001[e51]	Class II	Lack of allocation concealment, lack of primary outcome
PT/OT	Miyai, 2012[e52]	Class I for 4-week results	N/A
PT/OT	Ilg, 2009[e73]	Class IV	No control group (LOE statement was Class III but current systematic review is under new grading system)
PT/OT	Ilg, 2010[e74]	Class IV	No control group
PT/OT	Januario, 2010[e75]	Class IV	No control group
PT/OT	Rodgers, 1999[e76]	Class IV	No control group
PT/OT	Milne, 2012[e77]	Class IV	No control group
PT/OT	Ilg, 2012[e78]	Class IV	No control group (outcome assessor was blinded to timing of video, but the 2011 process manual amendments say that articles are Class IV if study "did not include patients receiving different interventions" and that is the case here)
PT/OT	Keller, 2014[e79]	Class IV	No control group
Stochastic vibration therapy	Kaut, 2014[e53]	Class III	Nonconcealed allocation. Procedures for allocation OK but used a pseudo-random sequence and so allocator could have quickly figured out sequence and manipulated it. Losses to follow-up not described. Need to assume that when they say that SARA was the primary outcome measure, they mean the SARA total score. Important baseline differences between groups that were not accounted for in statistics (e.g., no between-group change scores/*p* values).
Ayurvedic (massage or head treatments in India)	Sriranjini, 2009[e80]	Class IV	No control group
DBS	Fasano, 2010[e81]	Class IV	No control group (all treated with DBS; "normal control" group not related to the systematic review question
DBS	Teixeira, 2015[e82]	Class IV	Case report

Plum blossom needle tapping at Jiaji acupoints	Zhang, 2016[e83]	Class IV	No evidence that outcome assessment was masked, objective, or performed by someone who is not a member of the treatment team (a requirement for Class III or above); also, no concealed allocation and primary outcome not defined
Question 3			
TMS	Shiga, 2002[e84]	Class II	Pseudo-randomized, no primary outcome
tDCS	Benussi, 2015[e85]	Class III	No allocation concealment, no primary outcome measure, no comparison of baseline characteristics for treatment/order groups

Abbreviations: 3,4-DAP: 3,4-diaminopyridine; DBS = deep brain stimulation; FA = Friedreich ataxia; ITT = intention to treat; LOA = level of evidence; OPCA = olivopontocerebellar atrophy; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; tDCS = transcranial direct current stimulation; TRH= thyrotropin-releasing hormone.

Appendix e-6. Study review process diagram


MEDLINE and EMBASE
1966 to 2016
9,195 Citation(s)
9,195 Non-Duplicate
Citations Screened
Inclusion/Exclusion
Criteria Applied
8826 Articles Excluded
After Title/Abstract Screen
369 Articles Retrieved
Inclusion/Exclusion
Criteria Applied
309 Articles Excluded
After Full Text Screen
28 Articles Excluded
During Data Extraction
32 Articles Included

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