Movement Disorders
CLINICAL PRACTICE
REVIEW

Treatment Options in Degenerative Cerebellar Ataxia: A Systematic Review

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Abstract: The etiology of cerebellar ataxia (CA) is heterogeneous and includes easily identified and often reversible causes (i.e., drug toxicity and vitamin B12 deficiency) as well as irreversible degenerative conditions. It is the latter that poses a significant therapeutic challenge for practitioners treating this population of patients. To date, there are no U.S. Food and Drug Administration–approved medications for the treatment of CA. The literature, consisting mostly of case reports, case series, and small clinical trials, is sparse and scattered. These studies are difficult to translate clinically because they often describe diverse study populations with various identified and unidentified genetic etiologies. In addition, the reported treatment duration is often brief, and it is uncertain whether any of these options provide substantially lasting benefits. In this article, we review published reports and studies to aid the practitioner counseling patients with degenerative ataxias.

Degenerative cerebellar ataxias (CAs) are a group of disorders associated with progressive degeneration of the cerebellum, and its afferent and efferent pathways, resulting in the impairment of both appendicular and axial motor control. Patients often present with complaints of clumsiness, speech changes, and unsteady gait. These disorders can be classified into three major groups. The first group is the acquired ataxias resulting from causes such as toxins (e.g., alcohol), immune-mediated disorders (e.g., paraneoplastic cerebellar degeneration), vitamin deficiency (e.g., vitamin E), chronic central nervous system (CNS) infections (e.g., Creutzfeld-Jakob disease), and superficial siderosis. The other two groups are the hereditary and nonhereditary degenerative ataxias.[1] The inheritance pattern of the known hereditary ataxia disorders includes autosomal-dominant, autosomal-recessive, X-linked, and mitochondrial transmission. However, many patients present without a family history and have an unidentifiable etiology.

The neurochemistry of CA is complex, suggesting a variety of possible targets for ataxia treatment. Though gamma-aminobutyric acid (GABA) and glutamate are the primary neurotransmitters associated with motor control, neurotransmitters such as serotonin, norepinephrine, acetylcholine, dopamine, and histamine are also responsible for normal cerebellar function, including motor learning.[2] Unfortunately, current practice offers no recommendations for first-line medical or physical therapy (PT).

Several variables may influence the mixed outcomes of treatment studies, including the heterogeneity of the studied populations and the small sample size. The scattered publications addressing ataxia treatment, in addition to the lack of widely accepted guidelines, make it challenging for physicians to guide management in patients seeking comprehensive treatment, including PT. In this article, we offer the clinician an overview of the literature.

To identify relevant publications, a PubMed search using the terms "treatments of cerebellar ataxias," "degenerative cerebellar ataxia treatment," and "treatment of hereditary cerebellar ataxia" was conducted. The search engine generated 2,317 publications. Publications were excluded if the etiology of ataxia was acquired. Medication treatments with unduly side effects were excluded. Randomized and open-label interventional studies as well as prospective and retrospective observational studies of supplements, medications, and PT were reviewed. Case reports and case series were reviewed as well. All reviewed studies had either a minimum two-physician assessment or used a standardized rating scale to assess ataxia. All journal articles reviewed were written in English.

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Medication Therapy in Progressive Ataxia

Riluzole

Riluzole has several mechanisms of action, including a direct, but noncompetitive, blockade of excitatory amino acid receptors, inhibition of glutamate release, inactivation of voltage-dependent sodium channels, and stimulation of a G-protein-dependent signal transduction.[3] It is hypothesized that, in patients with CA, riluzole activates calcium-dependent potassium channels, causing inhibition of deep cerebellar nuclei and decreasing cerebellar hyperexcitabililty.[4]

One published study provided class I evidence for the use of riluzole in ataxia treatment. Subsequently, the use of riluzole received level B recommendations from the European Federation of Neurological Societies [4,5] In a double-blind, placebo controlled trial, patients in the treatment arm received 100 mg of riluzole (divided into twice-daily dosing) versus placebo. The 39 study participants were evaluated over an 8-week period. Patients receiving riluzole had a significant decrease of at least 5 points on the ICARS (International Cooperative Ataxia Rating Scale). This is a 100-point scale measuring static motor control, kinetic motor control, dysarthria, and oculomotor findings. The subgroup analysis showed improvement in static motor control, kinetic motor control, and dysarthria. Limitations to this study were: (1) a heterogeneous population, which included Friedreich's ataxia (FA), MSA-cerebellar variant (MSA-C), and autoimmune ataxias; (2) a small of number of patients; and (3) a short observation period.[4] In addition, the ICARS is not as effective as the SARA (Scale for Assessment and Rating of Ataxia), which is a bedside tool that rates ataxia-related symptoms, for the linear measurement of patient function.[4,6]

Antiglutaminergic Medication

Amantadine inhibits N-methyl-D-aspartate glutamate receptors, closes fast-opening calcium channels, and decreases calcium efflux. A study of 13 children with ataxia telangiectasia (AT; mean age: 11.2 years) showed mild-to-moderate improvement in symptoms of ataxia and parkinsonism when prescribed 7 mg/kg per day of amantadine. The primary endpoint was a decreased AT score, a composite of the ICARS, UPDRS, and the abnormal involuntary movement scale. Eleven patients demonstrated mild improvement (a 20%–39% decrease in the total AT score) and 2 had moderate improvement (40%–59% reduction) after 8 weeks of treatment. However, this reduction in AT scores was not sustained in the 9 patients who continued taking medication for 6 to 12 months. The secondary endpoint analysis suggested a significant improvement in gait, tremor, and dysmetria. Patients who discontinued amantadine after the initial assessment declined in all measures of the AT score.[7]

In another study comparing the efficacy of amantadine in 30 patients with olivopontocerebellar atrophy (OPCA) and 27 with FA, those with OPCA had a better response, compared to those with FA, in measures of simple visual and auditory reaction time and effective motor function over the 3- to 4-month study period. There was no control group. This study suggests that amantadine may improve symptoms of OPCA.[8]

Nicotine Receptor Agonists

Varenicline, a partial A4B2 nicotine receptor agonist, may modulate the activity of both Purkinje cells (PCs) and granule cells. It also acts on other nicotinic receptors, including the α-7 receptor. Action on these receptors may protect against glutamate-induced motor neuron death.

Small studies have reported successful use of varenicline in patients with autosomal-dominant CA. Eighteen SCA type 3 (SCA3) patients were recruited to participate in a randomized, double-blind, placebo-controlled study. Patients in the study arm received 1 mg twice-daily (BID) dosing. Assessments were made using the SARA. A significant improvement in gait, stance, and rapid alternating movements was noted. In addition, patients improved on the 25-foot timed walk test. Scores on the Beck Depression Inventory (BDI) improved in the treatment group as well. Four of the nine patients receiving placebo drug dropped out of the study. The small sample size and high placebo drop-out rate were limitations. However, this study provided class II evidence for the use of varenicline in the treatment of SCA3 patients.[9]

A follow-up study tested varenicline in a mixed ataxia population consisting of 3 patients with SCA3, 1 with MSA-C, and 3 with ataxia of unknown etiology.[10] There was no significant improvement with treatment. However, 5 of the 7 patients dropped out because of side effects. Clinical rating scales were not used. Contradictory study findings support the need for larger trials.

Serotonergic Therapy

Serotonin likely inhibits glutaminergic tone in the molecular layer of the cerebellum, potentially modulating cerebellar circuitry involved in motor control. A randomized, placebo-controlled study of 30 patients with both inherited and sporadic ataxias contained a treatment arm in which patients received 10 mg/kg per day of levorotatory hydroxytryptophan.[11] A total ataxia score consisting of eight static tests and six kinetic tests was used to assess benefit. Subtests assessed gait, presence of nystagmus, and performance on finger-to-nose testing. Patients were assessed before and after 4 months of treatment. Statistical analysis suggested benefit in time to walk, time standing upright with feet together, time to say a sentence, and time to write a name. Although this initial study demonstrated positive measures in gait, stance, writing, and speaking, subsequent studies with tryptophan found no benefit.[12,13]

Early studies of buspirone, a serotonin (5-HT)1A agonist, 60 mg/day in divided doses demonstrated positive results in adult-onset SCAs of unknown genetic etiology.[14–16] Each study included approximately 20 participants. These studies reported clinical improvement in lower body ataxia symptoms, such as

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time to standing upright. Some patients had improvements in gait, whereas posture control improved in others. However, a later randomized, double-blind, placebo-controlled study of 20 patients with varying etiologies (SCAs and FA) did not demonstrate a significant clinical benefit. Ultimately, no definitive conclusion can be made from these studies.[17,18]

A large, open-label trial of tandospirone, a 5-HT1A agonist, reported mixed results. Thirty-nine patients received 15 mg of tandospirone daily for 4 weeks. A subset of patients, those with SCA3 and SCA6, showed significant improvements in both the ataxia rating scale (ICARS) and depression assessments. This was not observed in the other patients with SCA1, SCA2, FA, or dentatorubro-pallidoluysian atrophy. The benefits in SCA3 and SCA6 patients were possibly a result of the preservation of the molecular layer of the cerebellar cortex in both conditions, because the molecular layer benefits most from serotonergic modulation. The other studied ataxias have significant destruction of the cerebellar cortical layer, likely limiting the effect of serotonergic medications.[19]

Other serotoninergic agents have not shown symptomatic benefit. Fluoxetine, a selective 5-HT receptor inhibitor, did not improve ataxia in 13 SCA3 patients. However, this study did not use a common ataxia rating scale. Instead, researchers assessed ataxia using the Kurtzke Functional Systems Scores, which is a multiple sclerosis rating scale that contains one item on cerebellar function. In addition, the Extended Disability Status Scale was used; this scale may be insensitive to gait changes in patients with difficulty walking. The UPDRS rating scale was used to assess parkinsonian symptoms often observed in SCA3.[20] The serotonergic antagonist, ondasetron, was tested in a randomized, double-blind study of 46 patients with diverse ataxia disorders. There was no statistically significant benefit in general ICARS scores in this group.[21] The benefit of serotonergic drugs in the treatment of ataxia is inconclusive, but several serotonergic drugs continue to be of interest for the treatment of CA.

GABAergic Therapy

Several case reports and small case series have reported a beneficial role of GABAergic drugs in adult patients with ataxia. Gabapentin stimulates alpha-2-delta P/Q calcium channels, enhancing GABA transmission. A small, open-label study looked at the role of gabapentin on 10 patients with cerebellar cortical atrophy (CCA) and 3 with hereditary ataxia of unknown etiology. CCA was defined as an SCA of unknown etiology with imaging evidence of isolated cerebellar atrophy. The study found immediate improvement in the ICARS score, in particular, in gait and body sway, after a single dose of 400 mg of gabapentin and again after 4 weeks of gabapentin with doses ranging from 900 to 1,600 mg daily [22].

Pregabalin, a GABA analog that binds to the alpha-2-delta subunit of P/Q voltage-gated calcium channels, 75 mg three times per day (TID) showed significant benefit in SARA scores in 2 patients with CCA. Larger, double-blind, placebo trials have not been performed to confirm these findings.[23]

A case series of 5 family members with SCA2 demonstrated improvement in ataxia symptoms with 10 mg of zolpidem, a drug that potentiates GABA.[24] Single-photon emission CT analysis in one of the family members displayed normalization of previous hypometabolism in the thalamus and cerebellum. The investigators did not report on the duration of treatment.

Lamotrigine may improve ataxia through GABA agonist activity, sodium channel blockade, and antiglutaminergic properties. A pilot, open-label study of lamotrigine in SCA3 suggested benefit in tandem gait and balance maneuvers, such as standing on one leg, at 10 weeks follow-up.[25]

Topiramate may improve ataxia by enhancing GABAergic transmission, antagonizing glutamate receptors, and stabilizing neuronal membranes in tremorogenic circuits. A case report discussed the benefit of this treatment in 1 patient with multiple sclerosis (MS) who had a large lesion burden in the posterior fossa. Before treatment, the patient had pronounced limb and trunk ataxia, dysarthria, horizontal nystagmus, and tremor of the head and proximal limbs. The tremor was prominent upon postural changes and during intentional movements and had a 3.3-Hz frequency. The patient was treated with 150-mg daily dosing of topiramate. She showed improvements in walking distance (up to 600 feet), truncal tremor, fine motor skills, and speech. Improvements were stable after 6 months of observation.[26]

Although the mechanism of levetiracetam is not fully understood, it is known to bind to SVC2, a binding protein, which may have long-range effects in the cerebral cortex, thalamus, and cerebellum. Cerebellar tremor may improve as a result of its effects on the ventralis intermedius nucleus of the thalamus or the thalamo-cortico-cerebellar loops. Because tremor can be quite bothersome and debilitating with inadequate treatments, mostly because of adverse effects, levetiracetam was tried in an open-label pilot study. Fourteen MS patients showed improvement on tremor rating scales and Archimedes spirals after 6 weeks of treatment of 50 mg/kg per day.[11] The researchers of this study did not describe the presence or absence of other features of cerebellar dysfunction. Levetiracetam did not improve other neurological conditions, and there was no relationship to disease duration or progression. Because the researchers did not address ataxia in this study, the role of levetiracetam in treating this symptom is unknown.

Cholinergic Therapy

Patients with CA may have cholinergic depletion, and it is thought that supplementation may improve symptoms. A small study tested the effect of transdermal physostigmine on 19 patients with ataxia, including those with idiopathic CA (iCA; n = 8) and those with autosomal-dominant SCAs (n = 11). From the latter group, 2 patients had SCA1 and 2 had SCA3. Thirty milligrams of transdermal physostigmine demonstrated no benefit in an ataxia rating scale that included assessments of gait, stance, finger-to-nose movements, eye movements, and speech. Thus, there is no evidence to recommend cholinergic therapy for ataxia patients at this time.[27]

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Channel Stabilizing Treatments

Because aminopyridines and acetozolamide were shown to have mild-to-moderate efficacy in patients with paroxysmal cerebellar ataxias from CACN1A mutations (episodic ataxia type 2; EA-2), the benefit of these treatments are of interest in SCA6, which results from a different mutation of the same gene that causes EA-2. It is proposed that 4-aminopyridine improves attacks in patients with EA-2 by blocking potassium channels, subsequently improving regulation of the PC pacemakers. Mouse models suggest this drug may increase the threshold for future attacks.[28,29] 3,4-diaminopyridine (DAP) was studied in 10 patients with SCA6 who were compared to 5 with 16q22.1-linked autosomal-dominant cerebellar ataxia. ICARS, posturography, and quantitative nystagmus measurements were performed before the medication was started and again after patients took 20 mg daily of DAP. Downbeat nystagmus improved, but there were no improvements in ataxia and balance.[30]

Acetozolamide, a carbonic anhydrase inhibitor, showed clinical benefit in a group of 9 patients with SCA6. Patients received 500-mg daily dosing. Improvements were noted in the Ataxia Rating Scale (ARS), stabilometry, and body sway during the 2-week titration period as well as the 8-week reassessment.[31]

Insulin-Like Growth Factor

Insulin-like growth factor-1 (IGF-1) acts as a neuromodulator in the CNS.[32] Disturbances in CNS signaling pathways may produce the pathophysiological changes that result in degenerative conditions, such as the SCAs. A 2-year prospective, open-label study of subcutaneous IGF-1 dosed at 0.05 mg/kg per BID was conducted in 7 SCA3 and 6 SCA7 patients. Total SARA scores improved after 8 months of treatment in SCA3 patients. SARA scores did not worsen in SCA7 patients at 20-month follow-up, interpreted by the study researchers as disease stabilization. Further large-scale studies are needed to confirm these results.

Supplements

Many patients are interested in alternative therapies and express a desire to pursue treatment with nonprescription medications. Antioxidants are one treatment approach tested in ataxia patients. Nine FA patients, ages 11 to 19 years, received idebenone 5 mg/kg per day for 12 months. ICARS was performed before treatment and every 3 months after starting the treatment for 1 year. There was improvement in the ICARS subscores for fine motor skills and eye movements. Patients with milder disease states and a lower number of triplet repeats also showed improvements in kinetic and gait function. Serum idebenone levels correlated negatively with the number of repeats, suggesting that more-affected individuals may need higher doses to achieve benefit. Of note, there was no improvement in echocardiography or neurophysiologic testing of the peripheral nervous system.[33]

Two large, randomized trials of idebenone in FA were subsequently performed. The earlier double-blind, placebo-randomized trial studied 48 patients with FA. Patients received placebo medication or 1 of 3 doses of idebenone (5, 15, and 45 mg/kg per day, divided into TID dosing). Randomization was stratified by weight and GAA repeat length. Although there was no significant difference in total ICARS scores, analysis suggested a dose-dependent response where patients who received the highest doses of idebenone did improve on the ataxia rating scale.[34] A later phase III, double-blind, placebo-controlled trial was conducted in 70 ambulatory FA patients receiving placebo versus idebenone. The dosing was based on body weight (≤45 mg/kg or >45 mg); the first group received a lower dose of either 450 mg/day versus 900 mg/day, divided into TID dosing. The second group received 1,350 or 2,250 mg of idebenone daily, again assigned based on body weight. At 6-month follow-up, patients who received idebenone did improve on ICARS scores, but the improvement was not statistically significant. It was ultimately concluded that idebenone did not significantly alter neurologic function, although follow-up duration was limited.[35] A 2012 Cochrane Database review concluded that no randomized, control trial has demonstrated benefit of idebenone in the treatment of FA.[36] The 2014 European Federation of Neurological Societies (EFNS) guidelines labeled idebenone as ineffective in the treatment of FA.[5]

Zinc may have a role in neural plasticity and development. Serum and cerebrospinal fluid levels of zinc are low in SCA2 patients.[37] A randomized, double-blind, placebo-controlled trial explored the role of zinc in the treatment of ataxia patients. Thirty-six SCA2 patients participated in the trial. The treatment arm received zinc 50 mg daily. Both placebo- and zinc-treated groups received neurorehabilitation as well, and it was hypothesized that zinc may act as an enhancer of neurorehabilitation. Of note, the neurorehabilitation provided to study patients was not described. Patients were followed for a 6-month period. Zinc and neurorehabilitation had no significant benefit, when compared to a combination of placebo and neurorehabilitation, in total SARA scores. However, a subgroup analysis demonstrated benefit in gait, stance, posture, and dysdiadochinesia in those who received zinc. Saccadic latency improved as well, and the researchers suggested this was the result of improvements in attention and processing associated with zinc supplementation.[37]

A recent open-label case series of 13 patients with various CAs demonstrated improvement in mean SARA scores after 1 week of acetyl-DL-leucine, 5 g per day. Given the low risk-benefit ratio, larger studies are warranted to further investigate the efficacy of this drug.[38]

Neurorehabilitation

The role of PT in CA is largely unknown. A study in The Netherlands assessed patient satisfaction and therapists' views of current PT strategies for treating ataxia patients. Results based on 317 patient questionnaires and 114 therapist questionnaires suggested that at least 64% of patients received PT, and nearly all patients reported at least a partial response to treatment; there was no statistical correlation between treatment frequency and reported

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effect. Nearly 20% of patients changed therapists because they felt they did not receive appropriate guidance; only 11% of therapists felt they had the expertise to treat ataxia patients. The researchers of this study concluded that evidence-based guidelines are necessary for the treatment of ataxia patients.[39]

A systematic review of allied health care for degenerative CA, including physical, occupational, and speech therapy, concluded that PT may improve ataxia symptoms and activities of daily living. The review identified 14 trials between 1980 and 2011. However, variable sample sizes, heterogeneity of diseases in study groups, and variations in the duration of therapies offered limit the generalizability of current neurorehabilitative studies to all ataxia patients.[40]

Since this review, several studies have explored the types of neurorehabilitation in the treatment of CA. A randomized, controlled trial tested the benefits of early versus late intervention of an intensive rehabilitation program. Forty-one patients with degenerative cerebellar disease and iCA with pure cerebellar dysfunction received 2 hours of PT and 1 hour of occupational therapy daily for 4 weeks. Patients were assessed at 0, 4, 12, and 24 weeks after treatment. Before therapy, patients could ambulate independently or with assistance for 10 minutes. Those in the immediate group received 24 weeks of in-patient rehabilitation after enrollment, whereas those in the delayed group started the same therapy 4 weeks later. SARA and a functional independence measure (FIM) were used for assessment. SARA scores in the immediate group versus the delayed group were better in terms of truncal ataxia, gait, stance, and decreased number of falls on FIM at 4 weeks. The immediate group also had greater gait speed than the delayed group. Though truncal ataxia and gait speed on SARA were sustained at 12 weeks, there was no continued decrease in the number of falls. At 24 weeks, overall improvement attenuated. Between the two groups, those with lower baseline SARA scores had sustained improvement. This suggests that those with milder ataxia were able to sustain their therapy-induced improvements better than those with more-severe ataxia. Those with milder forms of ataxia may have a greater capacity for motor learning.[41,42]

Video games were used for PT in 10 ambulatory children with degenerative ataxias. Patients received 2 weeks of intensive physiotherapy with a therapist, followed by 6 weeks of directed therapy using a video game. The video game stressed goal-directed limb movements, dynamic balance, and whole-body coordination. Children were also asked to react to virtual environments. Three Xbox games were used: Table Tennis; Light Race; and 20,000 Leaks. SARA posture scores and dynamic gait index improved after treatment. Gait analysis showed decreased step variability and lateral sway, suggesting decreased risk for falls. All improvements correlated with intensity of training. This study suggests an alternative, potentially beneficial means of physiotherapy for children.[43] Although no studies in adults currently exist, video games may be therapeutic options for adults.

A 2013 consensus paper on the management of degenerative CA treatments concluded its remarks on neurorehabilitation by stressing the need for effective long-term strategies to continue to maintain functionality, which included evaluating not only ambulating patients, but also those with more-severe disease, assessing predictive factors to determine who will most benefit from rehabilitation, and utilizing functional imaging to assess the effects of physiotherapy on cerebellar neural plasticity.[44]

Future Directions

Recruitment is ongoing for several trials assessing the efficacy of treatments, including riluzole, transcranial magnetic stimulation (TMS), mesenchymal stem cells (MSCs), and supplements, such as vitamin B3. The role of noninvasive cerebellar stimulation, either through TMS or direct current stimulation, is a promising option in treating conditions of cerebellar malfunction, such as tremor.[44] The likely mechanism is through TMS-induced cerebellar inhibition of deep nuclei by activation of PCs, leading to diminished excitatory input to the motor cortex.[45] A case report of a 62-year-old woman with iCA who received 21 consecutive days of TMS at 30 pulses per session demonstrated improved gait and postural stability, as noted on such tests as the Timed Get Up and Go and body sway measurements, both at day 21 and after 6 months of treatment. Improvements in speech and in the performance of dual simultaneous tasks were noted as well. Large-scale studies are needed to determine its role in treating ataxia patients on a continuing basis.

A previous study of 24 SCA (n = 14) and MSC-C (n = 10) patients who received one treatment of intrathecal umbilical cord mesenchymal stromal cells concluded that intrathecal injection was safe and could possibly delay neurological deficits in these patients.[46] Currently, there are two active studies assessing the efficacy of MSCs for hereditary CAs.

Two studies are assessing the effect of a novel form of thyrotropin-releasing hormone (KPS-0373) in degenerative SCAs. Other studies have either completed or begun recruitment for rehabilitation in ataxia. For more details, we recommend that practitioners visit www.clinicaltrials.gov.

Box 1 Summary points

1. Degenerative ataxias have a complex pathophysiology.
2. Effective treatment options are limited. Riluzole, amantadine, and varenicline have the best evidence despite the limitations in their studies.
3. Studies consist of small, heterogeneous patient samples and varied follow-up times.
4. Physical therapy is important, but appropriate strategies and guidelines are necessary for effective treatment.
5. Supplements and transcranial neuromodulation provide alternative treatment options, but larger studies are necessary for further recommendations.
6. Several clinical trials are ongoing in ataxia patients, testing diverse treatment options, including MSCs.

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TABLE 1 Medications with potential benefits in ataxia

Therapy (Class Evidence)	Trial Dosing of Oral Medication	Study Population (No. of Patients)	Study Type	Rating Scales	Clinical Ataxia Outcomes	Common Adverse Events
Riluzole[4] (level B)[5]	50 mg BID/day	Mixed (38)	Randomized, double-blind, placebo-controlled	ICARS	Improved static (gait), kinetic (tremor), and dysarthria subscores	Elevated liver ALT, vertigo
Varenicline [9] (level B) [5]	1 mg BID	Only SCA3 (18)	Randomized double-blind placebo controlled	SARA, 25-foot timed walk test, BDI	Improved gait, stance, and rapid alternating movements on SARA, lower BDI, and faster times on 25-foot walk test	Nausea, vivid dreaming, leg tingling
Amantadine [7,8] (level C) [5]	7 mg/kg per day	Only AT (13)	Open label, prospective	1. ICARS 2. UPDRS 3. Abnormal involuntary movement scale	Improved total composite scores and improved static, kinetic components of ICARS and bradykinesia of UPDRS	Constipation, sleepiness, headache, rash
	200 mg/day	Mixed (OPCA vs. FA) (57)	Double-blind, randomized trial	1. Simple visual and auditory mean reaction time 2. Movement time	Improvements in both reaction and movement time for OPCA, but *not* FA	Appetite loss, nightmares, mood changes
Gabapentin*[22]	400 mg × 1 then 900 to 1,600 mg daily	Mixed (13)	Open-label study	ICARS	Improvements in gait and body sway	Mild transient giddiness, abdominal pain, and impotence
Pregabalin*[23]	75 mg TID	Only CCA (2)	Single-blind, placebo-controlled study	SARA	Improvements of overall SARA scores	None reported
Zolpidem*[24]	10 mg/day	Only SCA2 (5)	Case series	No formal scales	4 of 5 had at least mild improvements in ataxia, tremor, and titubation	None reported
Lamotrigine*[25]	Not reported	Only SCA3 (6)	Open-label, self-controlled	1. One leg standing test 2. Tandem gait index	Tandem gait and balance (such as standing on one leg)	None reported
Topiramate*[26]	150 mg/day	Multiple Sclerosis (1)	Case report	Expanded Disability Status Scale	Improvements in total distance walked, speech, cerebellar tremor, and fine motor skills	None reported
Acetozolamide* [31]	500 mg/day	Only SCA6 (6)	Open-label prospective	1. ARS 2. Stabilometry	Improvements in total ARS, gait, and diminished body sway	Mild transient hand dysesthesia, asymptomatic mild hypotension, ureteric calculus
IGF-1* [32]	0.05 mg/kg per BID	Mixed (13)	Open-label prospective	SARA	Improved total SARA in SCA3 by 8 months and no clinical change in SCA7	None reported
Acetyl-DL-leucine*[38]	5 g/day	Mixed (13)	Open-label case series	SARA	Decreased total SARA scores with specific improvements in gait, finger chase, finger-to-nose, heel-to-shin, speech, and rapid alternating movements	None reported

*No existing level of recommendation, insufficient data for recommendation.

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Conclusions

CA is the result of a wide range of pathophysiologic mechanisms. Various treatment options for ataxia are explored in the literature, and physicians should be prepared to discuss treatment options with their patients seeking therapy (Box 1). Although there is no cure for these conditions, small studies suggest that some medications (Table 1) and physical therapy can improve ataxia symptoms. These studies are limited by heterogeneous patient populations, small study groups, and short duration of follow-up. Similar to recommendations made in previous reviews of CA, we advocate the need for large-scale studies with more-homogenous study groups.[47]

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

H.S.: 1A, 1B, 1C, 3A

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