Comprehensive Systematic Review: Treatment of Cerebellar Motor Dysfunction and Ataxia

Summary for Comments from the Public


This document is meant to serve as a public summary of the American Academy of Neurology (AAN) comprehensive systematic review (SR) “Treatment of Cerebellar Motor Dysfunction and Ataxia.” This summary was created as a way for individuals (1) to better understand the material contained in the full document and (2) to provide their feedback during the AAN’s public comment period for this SR. This SR follows the approach described in the AAN’s 2004 process manual (available at https://www.aan.com/Guidelines/Home/UnderDevelopment). The SR also uses an updated process for grading scientific evidence in the study of therapies (available in the amendments to the 2011 process manual at https://www.aan.com/Guidelines/Home/Development).

The complete SR is available at www.aan.com/practice-guidelines/home/public-comments.

For more information on the levels of evidence, see the table at the end of this document.
INTRODUCTION

The part of the brain called the cerebellum plays a large part in balance and body movement. The cerebellum may not work properly for many reasons, such as:

- Hereditary lack of voluntary muscle control due to genetics (passed down through parents’ genes)
- A lack of needed vitamins in the body
- Tumors
- Infections
- Inflammation
- Stroke
- Multiple sclerosis
- Toxins
- Gradual loss of nerve cells

Symptoms resulting from the cerebellum not working normally may include some or all of the following:

- Ataxia (clumsiness, loss of full control of bodily movements)
- Dysarthria (difficulty speaking clearly)
- Lack of balance, reduced coordination, and limb or body shaking
- Unusual eye movement

Sometimes diseases affecting the cerebellum also affect other parts of the nervous system and cause other symptoms such as:

- Dystonia (involuntary muscle tightening that causes repeated or twisting movements)
- Muscle weakness
- Neuropathy (tingling sensation, pain, or numbness, usually in hands or feet)
- Symptoms of Parkinson disease
- Sensory difficulties (trouble with seeing, hearing, smelling, etc.)
- Mood problems (depression, anxiety)
- Difficulties with the body’s automatic functions

At this time there is no approved therapy, drug, or operation to treat cerebellar dysfunction. There is also no drug or operation that is regularly used as the standard of care. Various treatments have been studied for the past 40 years. There is not agreement on the effectiveness of the treatments.
This SR looks at the following questions:

1. For patients with cerebellar movement problems, do prescription drug therapies improve movement symptoms in a safe and bearable (tolerable) way?

2. For patients with cerebellar movement problems, do surgical or other therapies (such as physical training) improve movement symptoms in a safe and bearable way?

3. For patients with cerebellar motor dysfunction, does the use of magnetic stimulation of nerve cells in the brain (transcranial magnetic stimulation [TMS]) improve movement symptoms in a safe and bearable way?

**ANALYSIS OF EVIDENCE**

**Prescription Drugs with Evidence of a Benefit**

The authors of the SR made the following conclusions, based on analysis of the evidence found, for prescription drugs that can help improve movement symptoms with acceptable safety and tolerability.

*4-aminopyridine (4-AP)*

There is moderate evidence* that for patients with a disease called episodic ataxia, 15 mg of 4-AP each day can help reduce the number of ataxia attacks over 3-months.

*Riluzole*

---

*How is evidence defined in an SR?*

The results of research studies are called *evidence*. In science and medical research, evidence is gathered through observations that happen the natural world, or which are created as experiments in a laboratory or other controlled conditions.

*What is a conclusion in an SR?*

Conclusions are summary statements about the evidence. They are based on the authors’ analysis of all the evidence found.
There is moderate evidence* that for patients with ataxia, 100 mg of riluzole each day can be effective for short-term treatment (8 weeks).

Thyrotropin Releasing Hormone (TRH)

There is weak evidence* that for patients with spinocerebellar degeneration, TRH may help improve some symptoms of ataxia over 10 to 14 days. It is uncertain if this therapy has a noticeable effect on daily life.

Prescription Drugs that Don’t Help Ataxia

The authors of the systematic review made the following conclusions, based on analysis of the evidence found, on prescription drugs that may not help improve movement symptoms.

Lithium Carbonate

For patients with spinocerebellar ataxia type 3 (SCA3) who are still able to walk, there is moderate evidence* that lithium probably does not improve ataxia over 48 weeks. However, it is possible that lithium could have a small effect on quality of daily living.

Deferiprone

For patients with Friedreich’s ataxia, there is weak evidence* that a 40 mg/kg dose of deferiprone each day may worsen ataxia symptoms over 6 months.

Prescription Drugs with Evidence Showing Conflicting Results
The authors of the systematic review concluded that the evidence on buspirone, tryptophan, or choline was conflicting (inconsistent). The authors determined there is not enough evidence* to show a benefit from any of these three drugs for the treatment of cerebellar movement problems.

Prescription Drugs with Not Enough Evidence

The authors determined there is not enough evidence* to show a benefit from the following drugs for the treatment of cerebellar movement problems:

- Varenicline
- Ondansetron
- Dolasetron mesilate
- Trimethoprim-sulfamethoxazole
- Zinc
- L-Carnitine
- Phystostigmine
- Amantadine
- Branched chain amino acids
- Betamethasone

Surgical or other therapies (such as physical training)

Pressure Splints

Pressure splints help lessen the tightening or stiffening of muscles. For patients with ataxia associated with multiple sclerosis, there is weak evidence* that adding pressure splints to an existing rehabilitation program for nerves and muscles may not provide added benefit over rehabilitation alone.

Physical and Occupational Therapy

For patients with isolated degenerative ataxias (ataxias related to gradually worsening changes in the brain), the authors determine there is moderate evidence* that 4 weeks of rehabilitation in a hospital setting with physical and occupational therapy can help improve control of bodily movement and functioning.
Stochastic Vibration Therapy

Stochastic vibration therapy devices vibrate (shake) the whole body. They are used to help strengthen muscles. The authors of the SR concluded that there is not enough evidence* to show if this therapy helps treat spinocerebellar ataxias.

Magnetic stimulation of nerve cells in the brain (transcranial magnetic stimulation [TMS])

The authors of the SR concluded there is weak evidence* that TMS may help improve movement symptoms at 21 days in patients with cerebellar diseases called spinocerebellar degeneration and olivopontocerebellar atrophy (OPCA).

DISCUSSION AND RECOMMENDATIONS FOR FUTURE RESEARCH

Future research in cerebellar movement problems should aim to look at different cerebellar diseases more closely, rather than grouping people with different cerebellar diseases together. This will help us learn if a treatment helps a specific kind of cerebellar disease. There should also be more research to find better treatments (drugs and other treatments) for either slowing down or stopping cerebellar diseases that get worse over time and treating the movement problems that happen with cerebellar diseases. Finally, the research studies should be designed well so that we know if the treatments help (for example, researchers need to enroll more people in each study and use more reliable tests).
Table 1: *Definitions for Levels of Evidence*

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong Evidence</td>
<td>There is more than one high-quality scientific study.</td>
</tr>
<tr>
<td>Moderate Evidence</td>
<td>At least one high-quality scientific study or two or more studies of lesser quality.</td>
</tr>
<tr>
<td>Weak Evidence</td>
<td>The studies, while supportive, are weak in design or strength of the findings.</td>
</tr>
<tr>
<td>Not Enough Evidence</td>
<td>Either different studies have come to conflicting results or there are no studies of reasonable quality.</td>
</tr>
</tbody>
</table>

This SR is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative approaches. The AAN recognizes that specific patient care decisions should be made by the patient and the physician caring for the patient based on all of the circumstances involved.

Table 2: Overview of SR Development Process

1. Authors identify one or more questions that need to be answered. The question(s) should address a topic that clinicians are unclear on or disagree on such as how to treat or diagnose a condition.

2. Authors find and evaluate all the evidence that applies to the question. They search the medical library databases to find the evidence. They examine the evidence they find, and rate (judge) its content and quality using AAN rules for grading.

3. Authors make statements that summarize the evidence (conclusions) to answer the question(s).