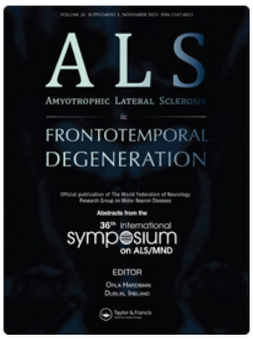

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REVIEW ARTICLE

ALSUntangled #81: Pyridostigmine (mestinon®)

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Abstract:
Pyridostigmine (Mestinon®, Bausch Health, Canada Inc.) increases acetylcholine availability at the neuromuscular junction, enhancing transmission. Preclinical studies suggest that neuromuscular junction dysfunction develops early in ALS, and pyridostigmine may temporarily improve neuromuscular transmission. However, altered neuromuscular junction transmission has uncertain benefits in ALS progression. Pyridostigmine does not have other plausible mechanisms that truly modify ALS pathophysiology. People with ALS (PALS) who have positive acetylcholine receptor autoantibodies and no myasthenia symptoms are unlikely to respond to pyridostigmine treatment. Clinical trials on pyridostigmine in PALS are lacking, but two clinical trials of other similar anticholinesterase agents did not effectively slow ALS progression. Muscarinic cholinergic side effects, including gastrointestinal symptoms, are common. Given the lack of mechanistic plausibility and efficacy, we do not support the use of pyridostigmine for slowing ALS progression.

Keywords: *Acetylcholinesterase inhibitor, motor neuron disease, amyotrophic lateral sclerosis, neuromuscular junction, off-label use*

Introduction

ALSUntangled reviews alternative and off-label treatments for people with amyotrophic lateral sclerosis (PALS). Here, we apply the ALSUntangled methodology (1) to systematically evaluate pyridostigmine for which we have had 67 requests.

Pyridostigmine is a reversible acetylcholinesterase inhibitor that blocks acetylcholine (ACh) breakdown, increasing its availability at the neuromuscular junction (NMJ). Pyridostigmine is commonly used to symptomatically treat myasthenia gravis (MG), a condition of autoimmune-mediated

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destruction of nicotinic acetylcholine receptors (nAChRs) located at the skeletal muscle surface (postsynaptic membrane) of the NMJ, leading to muscle weakness (2). Although ALS primarily involves motor neuron degeneration, NMJ alterations have been observed, suggesting potential benefits from therapies targeting NMJ function (3–5). However, the efficacy and safety of pyridostigmine in PALS remain uncertain, and its use in this context is not well-established.

Mechanistic plausibility

In ALS, the primary pathology involves the progressive degeneration of upper and lower motor neurons, leading to muscle spasticity, weakness and atrophy. While ALS is not primarily a disorder of ACh or nAChR, studies in preclinical models have shown that NMJ dysfunction and denervation occur early in ALS, even preceding motor neuron loss (6,7). Additionally, although AChR autoantibodies are primarily associated with MG, they have also been detected in ALS patients without clinical signs of MG, and one study even reported increasing autoantibody titers in an ALS patient as the disease progressed (8,9).

Pyridostigmine increases ACh levels at the NMJ, facilitating signal transmission between nerves and muscles. Theoretically, this drug could transiently enhance neuromuscular transmission in early-stage ALS with preserved motor neurons and dysfunctional NMJ. However, as ALS advances and motor neurons degenerate more widely, this theoretical benefit of increasing ACh at NMJs diminishes.

Since pyridostigmine may transiently improve neuromuscular transmission in early ALS but does not have relevant mechanisms that could alter the disease process, ALSUntangled assigns a Table of Evidence (TOE) "Mechanistic Plausibility" grade of D (Table 1).

Preclinical models

We found no studies of pyridostigmine in preclinical ALS models. A study investigated the effect of neostigmine, another cholinesterase inhibitor similar in mechanism to pyridostigmine, in a mutant $SOD1^{G93A}$ mouse model of ALS. Neostigmine treatment exacerbated clinical parameters in $SOD1^{G93A}$ mice, with a more rapid motor function decline, accelerated disease progression, and shorter survival compared to untreated controls (10).

Since pyridostigmine has not been studied directly in pre-clinical models, ALSUntangled assigned a TOE "Pre-clinical" grade of U (Table 1).

Cases

ALS may be misdiagnosed as MG because both conditions manifest as muscle weakness; this occurs mainly in bulbar onset ALS or when the presenting symptom is neck extension weakness (dropped head syndrome). Moreover, repetitive nerve stimulation (RNS), a diagnostic electrophysiological test for MG, can be positive in ALS (11,12). A low titer AChR antibodies may be detected in PALS (9). However, studies show that PALS who have positive RNS test and AChR antibodies (but lack typical MG symptoms such as ptosis, diplopia, and fatigable weakness) typically do not respond to pyridostigmine treatment (8). Short-term improvements in bulbar weakness (lasting days to weeks) during the early stages of the disease were previously reported (13). However, this short-term benefit in PALS remains anecdotal.

On the other hand, two cases of ALS with ocular ptosis, a rare symptom in ALS, were treated with pyridostigmine, which did not result in any clinical benefits (14). Notably, both patients had normal RNS tests and were negative for AChR antibodies.

Although the coexistence of MG and ALS is rare, several cases have been reported (8,15–18). For instance, a patient with a positive ALS family history was diagnosed with ALS after he developed atrophy and weakness in the right hand with associated diffuse muscle fasciculations and cramps. His neurological examination and EMG revealed both upper and lower motor neuron signs in the cervical and lumbar regions. In three months after the ALS diagnosis, he developed ptosis, diplopia and

Table 1. Table of evidence for pyridostigmine.

Criteria	Grade	Comments
Mechanistic Plausibility	D	Pyridostigmine may transiently improve neuromuscular transmission in early ALS but does not have relevant mechanisms to alter the disease process.
Pre-clinical models	U	There are no studies of pyridostigmine in pre-clinical models. A study of another cholinesterase inhibitor, neostigmine, worsened outcomes in an *SOD1*-ALS rodent model.
Cases	B	Although most cases showed no benefits from pyridostigmine on ALS progression, two validated ALS reversal cases took pyridostigmine as part of their treatment regimens.
Trials	U	There have not been clinical trials of pyridostigmine in PALS and trials of other cholinesterase inhibitors did not slow ALS progression.
Risks	C	Pyridostigmine causes frequent cholinergic side effects due to the increased acetylcholine levels.

fatigable weakness, which was reversed by rest (15). Serology testing showed an elevated AChR antibody concentration of 22.5 pmol/L (normal value <0.4 pmol/L). RNS test revealed a decremental response greater than 40% in ocular and deltoid muscles. This patient's ocular symptoms improved with pyridostigmine. Another case initially presented with speech and swallowing difficulties (16). MG diagnosis was made after a clinical examination, with positive AChR antibodies, decremental responses on RNS test and a positive edrophonium test. His symptoms improved with prednisone and pyridostigmine treatment. However, five months later, he presented with new symptoms of tongue atrophy and fasciculations and neck and limb muscle weakness. His neurological examination demonstrated hyperreflexia that was not present previously, as well as new bulbar and limb muscle atrophy and weakness. Repeat electromyography showed widespread active denervation and chronic reinnervation changes, supporting an ALS diagnosis. In both aforementioned cases, their MG symptoms responded to pyridostigmine as expected.

Another interesting study examined the benefits of a presynaptic NMJ transmission enhancing medication, 3,4 diaminopyridine (DAP), in PALS and found that 3,4 DAP treatment improved self-reported fatigue and muscle weakness compared to placebo group (19).

Additionally, anecdotal reports from an online forum (ALSforums.com) suggest that some ALS patients have been prescribed pyridostigmine, with one individual reporting a perceived slowing of disease progression. On PatientLikeMe, five PALS reported taking pyridostigmine, and only one patient provided an evaluation, reporting "can't tell."

Within the cohort of 62 validated "ALS Reversals" being referred to Duke University for participation in the ALS reversal study (https://als-reversals.com), two were on pyridostigmine (in addition to many other medications and supplements) when their recovery occurred. It is impossible to know whether pyridostigmine contributed to their recovery. Within the ALS Therapy Development Institute's ALS research collaborative database (https://www.als.net/arc/), four additional individuals reported using pyridostigmine either before or during their participation in this longitudinal study. No clear benefit of pyridostigmine on ALSFRS-R progression was seen.

PALS may develop dysautonomia symptoms such as gastric paresis, orthostatic hypotension and urinary problems (20,21). Though pyridostigmine has been shown to improve gastrointestinal motility (22), it often increases oral and bronchial secretions and risks for aspiration. We therefore caution for the use of pyridostigmine for gastric paresis and other dysautonomic symptoms.

Although most cases we found showed no benefits from pyridostigmine on ALS progression, two validated ALS reversal cases took pyridostigmine as part of their treatment regimens as mentioned above. Therefore, we assign a TOE "Cases" grade of B (Table 1). However, we caution that this is an association, and we cannot know whether pyridostigmine contributed to the ALS reversals.

Trials

We found no clinical trials specifically evaluating pyridostigmine for PALS. Therefore, ALSUntangled assigned a TOE "Trials" grade of U (Table 1).

Of interest, however, other acetylcholinesterase inhibitors were evaluated in two small placebo-controlled, randomized clinical trials (23,24). A 9-month double-crossover trial was conducted in 1993 to assess the effects of oral physostigmine, an acetylcholinesterase inhibitor that penetrates the blood-brain barrier (23). During this study, participants were randomly assigned to either the physostigmine or placebo group for 3 months, then crossed over to the other group for an additional 3 months and returned to their originally assigned group for a final 3 months. Twenty-five participants were randomized, but twelve dropped out of the study due to death, severe disability or severe swallowing difficulty. Among thirteen participants who completed the 9-month study, five participants received physostigmine (16 mg daily) in the first and third 3-month periods, and eight received 16 mg daily in the second 3-month period. The Norris ALS score (similar to the ALS functional rating scale), forced vital capacity and survival were assessed after each 3-month period, but did not show slowing of ALS progression (23). Another study in 1986 compared physostigmine and neostigmine in terms of their effects on muscle strength and neurophysiology in PALS but did not show any differences (24).

Risks

Pyridostigmine is generally well-tolerated but can cause side effects, mostly related to the increased muscarinic acetylcholine signaling. Common side effects include gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal cramps, increased salivation, bronchial secretions, increased sweating, muscle cramps, twitching, blurred vision, and lightheadedness (25). In rare cases, excessive dosing may paradoxically worsen weakness, a rare condition known as cholinergic crisis in patients with myasthenia gravis (26).

ALSUntangled assigns a TOE "Risk" grade of C (Table 1).

Dosing and costs

Pyridostigmine is commonly used to manage myasthenia gravis symptoms at a dose of 60–90 mg every 4–6 hours while awake (180–240 mg daily) due to the medication's short duration of action (26). An extended-release formulation of pyridostigmine is also available but is infrequently used. It is important to note that the appropriate dosing for ALS patients has not been established.

Pyridostigmine is available as a generic form and is relatively inexpensive. The cost varies depending on dosage and formulation, and a 90-tablet supply of pyridostigmine 60 mg tablets generally ranges from $20 to $30 without insurance.

Conclusion

Pyridostigmine has a plausible mechanism for transiently enhancing neuromuscular transmission in early-stage ALS, where NMJ transmission is impaired but motor neuron numbers are preserved. However, there is no plausible mechanism for slowing ALS progression. Case reports showed PALS without typical MG symptoms did not respond to pyridostigmine. Thus far, clinical trials of pyridostigmine in PALS have not been conducted. Two small clinical trials of other cholinesterase inhibitors failed to show efficacy in PALS.

Additionally, pyridostigmine carries potential, albeit mild, risks, including gastrointestinal side effects and excessive salivation at recommended doses. Given the lack of mechanistic plausibility and efficacy in case reports, we do not support the use of pyridostigmine as a pharmacological agent for slowing ALS progression.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

1. ALSUntangled: introducing the table of evidence. Amyotroph Lateral Scler Frontotemporal Degener. 2015; 16:142–5.
2. Maggi L, Mantegazza R. Treatment of myasthenia gravis: focus on pyridostigmine. Clin Drug Investig. 2011;31:691–701.
3. Bruneteau G, Bauché S, Gonzalez de Aguilar JL, Brochier G, Mandjee N, Tanguy ML, et al. Endplate denervation correlates with Nogo-A muscle expression in amyotrophic lateral sclerosis patients. Ann Clin Transl Neurol. 2015;2:362–72.
4. McIntosh J, Mekrouda I, Dashti M, Giuraniuc CV, Banks RW, Miles GB, et al. Development of abnormalities at the neuromuscular junction in the SOD1-G93A mouse model of ALS: dysfunction then disruption of postsynaptic structure precede overt motor symptoms. Front Mol Neurosci. 2023;16:1169075.
5. Piol D, Robberechts T, Da Cruz S. Lost in local translation: TDP-43 and FUS in axonal/neuromuscular junction maintenance and dysregulation in amyotrophic lateral sclerosis. Neuron. 2023;111:1355–80.
6. Fischer LR, Culver DG, Tennant P, Davis AA, Wang M, Castellano-Sanchez A, et al. Amyotrophic lateral sclerosis is a distal axonopathy: evidence in mice and man. Exp Neurol. 2004;185:232–40.
7. Altman T, Ionescu A, Ibraheem A, Priesmann D, Gradus-Pery T, Farberov L, et al. Axonal TDP-43 condensates drive neuromuscular junction disruption through inhibition of local synthesis of nuclear encoded mitochondrial proteins. Nat Commun. 2021;12:6914.
8. Tai H, Cui L, Guan Y, Liu M, Li X, Huang Y, et al. Amyotrophic lateral sclerosis and myasthenia gravis overlap syndrome: a review of two cases and the associated literature. Front Neurol. 2017;8:218.
9. Okuyama Y, Mizuno T, Inoue H, Kimoto K. Amyotrophic lateral sclerosis with anti-acetylcholine receptor antibody. Intern Med. 1997;36:312–5.
10. Gotkine M, Rozenstein L, Einstein O, Abramsky O, Argov Z, Rosenmann H. Presymptomatic treatment with acetylcholinesterase antisense oligonucleotides prolongs survival in ALS (G93A-SOD1) mice. Biomed Res Int. 2013;2013:845345.
11. Kim JY, Park KD, Kim SM, Sunwoo IN. Repetitive nerve stimulation test in amyotrophic lateral sclerosis with predominant oropharyngeal manifestations. J Clin Neurol. 2011;7:31–3.
12. Denys EH, Norris FH. Jr. Amyotrophic lateral sclerosis. Impairment of neuromuscular transmission. Arch Neurol. 1979;36:202–5.
13. Borasio GD, Voltz R. Palliative care in amyotrophic lateral sclerosis. J Neurol. 1997;244 Suppl 4:S11–S17.
14. Pinto S, de Carvalho M. Amyotrophic lateral sclerosis patients and ocular ptosis. Clin Neurol Neurosurg. 2008; 110:168–70.
15. Restivo DA, Bianconi C, Ravenni R, De Grandis D. ALS and myasthenia: an unusual association in a patient treated with riluzole. Muscle Nerve. 2000;23:294–5.
16. Hodzic R, Piric N, Zukic S, Cickusic A. Coexistence of myasthenia gravis and amyotrophic lateral sclerosis in a Bosnian male: an unusual clinical presentation. Acta Myol. 2021;40:66–8.
17. Greenblatt AS, Chen IA. Pearls and Oy-sters: Myasthenic Crisis in a Patient With Motor Neuron Disease: Hickam's Dictum vs Occam's Razor. Neurology. 2022;98:378–81.
18. 46th Annual Carrell-Krusen neuromuscular Symposium, Dallas, TexasThursday–Friday, February 22–23, 2024: Meeting Convener: Susan T. Iannaccone, MD, FAAN. J Clin Neuromuscul Dis. 2024;25(1S):S1–S19.
19. Bertorini TE, Rashed H, Zeno M, Tolley EA, Igarashi M, Li YD. Effects of 3-4 Diaminopyridine (DAP) in Motor Neuron Diseases. J Clin Neuromuscul Dis. 2011;12:129–37.
20. Quarracino C, Capani F, Otero-Losada M, Rodríguez GE, Pérez-Lloret S. Frequency of orthostatic hypotension in the pooled resource open-access ALS clinical trials database. Front Neurol. 2025;16:1512357.

21. Dubbioso R, Provitera V, Pacella D, Santoro L, Manganelli F, Nolano M. Autonomic dysfunction is associated with disease progression and survival in amyotrophic lateral sclerosis: a prospective longitudinal cohort study. J Neurol. 2023;270:4968–77.
22. Bharucha AE, Low PA, Camilleri M, Burton D, Gehrking TL, Zinsmeister AR. Pilot study of pyridostigmine in constipated patients with autonomic neuropathy. Clin Auton Res. 2008;18:194–202.
23. Norris FH, Tan Y, Fallat RJ, Elias L. Trial of oral physostigmine in amyotrophic lateral sclerosis. Clin Pharmacol Ther. 1993;54:680–2.
24. Aquilonius SM, Askmark H, Eckernäs SA, Gillberg PG, Hilton-Brown P, Rydin E, et al. Cholinesterase inhibitors lack therapeutic effect in amyotrophic lateral sclerosis. A controlled study of physostigmine versus neostigmine. Acta Neurol Scand. 1986;73:628–32.
25. Remijn-Nelissen L, Verschuuren J, Tannemaat MR. The effectiveness and side effects of pyridostigmine in the treatment of myasthenia gravis: a cross-sectional study. Neuromuscul Disord. 2022;32:790–9.
26. Farrugia ME, Goodfellow JA. A practical approach to managing patients with myasthenia gravis-opinions and a review of the literature. Front Neurol. 2020;11:604.