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ALSUntangled 57: Vinpocetine

THE ALSUNTANGLED GROUP

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RESEARCH ARTICLE

ALSUntangled 57: Vinpocetine

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ALSUntangled reviews alternative and off-label treatments on behalf of people with ALS (PALS). Here we review Vinpocetine for which we have had over 600 requests (1).

Overview

Vinpocetine (chemical name 14-ethoxycarbonyl-(3a,16a-ethyl)-14,15-eburnamine) is a product derived from an alkaloid substance in the periwinkle plant *Vinca minor* (2). In many countries it is classified as a prescription drug and is used for the treatment of acute stroke and cognitive impairment (3), although systematic reviews have failed to confirm any benefits for patients with these conditions (4,5). In the Unites States, it is classified as a nutritional supplement (3). At least one website claims that Vinpocetine might be "beneficial for ALS" (6). A published case series demonstrated that Vinpocetine was associated with reduced cramping in PALS and suggested further study, including determining whether it could slow ALS progression (7). This review examines Vinpocetine's potential role in slowing ALS progression.

Mechanistic plausibility

Orally and intravenously administered Vinpocetine enters the CSF and brain (8). There it may plausibly affect at least 5 ALS mechanisms: hyperexcitability, excitotoxicity, oxidative stress, neuroinflammation and mitochondrial dysfunction.

Hyperexcitability

Cortical hyperexcitability, as measured by transcranial magnetic stimulation, is common across genetic and sporadic ALS subtypes (9), precedes the onset of lower motor neuron dysfunction and weakness (10), and correlates anatomically with the pattern of disease spread (11). Causes of cortical hyperexcitability include increased motor neuron sodium currents (12); riluzole may exert some of its survival benefit by reducing these currents (13). Vinpocetine can block neuronal voltage gated sodium channels (2,14), potentially reducing sodium currents and cortical hyperexcitability.

Excitotoxicity

We previously reviewed glutamate-induced neurotoxicity mediated via AMPA receptors as an ALS mechanism (15). Vinpocetine can block AMPA receptors and protect cultured cortical neurons against excitotoxicity (16,17). Riluzole may exert some of its survival benefit via decreasing excitotoxity (18). Unfortunately, three other drugs that act on this pathway failed to help PALS in trials (19–21).

Oxidative stress

As discussed in a recent ALSUntangled paper, oxidative stress may contribute to ALS progression (22). While clinical trials of most antioxidants have shown no benefits (23,24), one trial found that Edaravone slightly slows disease progression in a subset of PALS (25). Vinpocetine can protect neuronal cultures from oxidative stress (26,27), and can decrease serum and tissue biomarkers of oxidative stress in a rat model of ischemia-reperfusion injury (28).

ALSUntangled Reviewers who contributed to this paper include the following: Richard Bedlack, Carmel Armon, Paul Barkhaus, Benjamin Barnes, Michael Bereman, Tulio Bertorini, Greg Carter, Amy Chen, Jesse Crayle, Merit Cudkowicz, Carlayne Jackson, Matthew Kiernan, Gleb Levitsky, Christopher McDermott, Gary Pattee, Erik Pioro, Kristiana Salmon, Kim Staats, James Stephens, Paul Wicks, others who contribute.
Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.
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Table 1. Table of Evidence for vitamin Vinpocetine.

	Grade	Explanation
Mechanism	A	Vinpocetine can enter the brain and affect 5 mechanisms that are believed to be important in ALS: hyperexcitability, excitotoxicity, oxidative stress, neuroinflammation and mitochondrial dysfunction. Its effects on neuroinflammation biomarkers have been demonstrated in a human trial.
Pre-Clinical	U	We found no studies of Vinpocetine in recognized pre-clinical models of ALS.
Cases	D	We found 2 PALS reporting that supplement cocktails including Vinpocetine were associated with improved motor function, but we did not have records to independently verify their diagnoses or improvements.
Trials	U	We found no trials of Vinpocetine in PALS.
Risks	D	More than 0 but less than 5% of exposed patients experienced serious adverse events.

Neuroinflammation

Neuroinflammation, including activation of the NF-κB cellular signaling pathway, may contribute to the pathophysiology of ALS (29–34). Downregulating this pathway is beneficial in mouse models of ALS (31–34). Trials of immune-modulating therapies have thus far been unsuccessful in PALS (35), with the possible recent exception of Masitinib (36). Vinpocetine can inhibit IκB kinase, ultimately downregulating NF-κB mediated neuroinflammation (2,37,38). In a trial of patients with Parkinson's disease, Vinpocetine treatment was associated with reductions in several inflammatory biomarkers including NF-κB, toll-like receptors and cytokines (39).

Mitochondrial dysfunction

Many lines of evidence implicate mitochondrial dysfunction in the pathophysiology of ALS (40). Vinpocetine may have potentially beneficial effects on mitochondrial membrane currents and energy production, at least in cell cultures and isolated mitochondria (41,42).

Based on Vinpocetine's ability to affect mechanisms believed to be important in ALS, including its ability to reduce biomarkers of neuroinflammation in a human trial, ALSUntangled assigns a "Mechanism" grade of "A" (Table 1).

Pre-clinical models

We found no studies of Vinpocetine in recognized pre-clinical models of ALS. Therefore ALSUntangled assigns a "Pre-Clinical" grade of "U" (Table 1).

Cases

In the online community PatientsLikeMe, nine people reported taking Vinpocetine for ALS; one completed detailed evaluations. At doses ranging from 5mg to 1000mg daily (43), they were unable to tell if it was helpful in any way. In the online forum ALS net, one person reported that a combination of supplements including Vinpocetine 400mg to 1000mg daily helped with "clarity of speech" (44). Another person reported that a supplement cocktail including Vinpocetine at 200mg to 1000mg daily was associated with improved dyspnea and increased arm and leg strength in their spouse who had ALS (44). We did not have medical records to independently verify the diagnoses or the reported improvements in these patients. One ALSUntangled reviewer (GL) cared for 11 PALS on Vinpocetine; they saw no obvious benefits. Based on this information, ALSUntangled assigns a "Cases" grade of "D" (Table 1).

Trials

We found no trials of Vinpocetine in PALS. Therefore we assign a "Trials" grade of "U" (Table 1).

Dosing, risks, costs

The optimal dose for PALS has not been established. In a case series of 27 PALS treated with Vinpocetine for cramps, the dose was 5mg three times daily for up to 24 months (7); no adverse events were noted. PALS online reported using 5mg to 1000mg per day (43,44). At these doses, some experienced side effects including dizziness, increased fasciculations, changes in body temperature and limb swelling (43,44). Human studies in patients with Parkinson's disease (39), stroke (45,46), cognitive impairment (47–49) and various other non-neurological conditions (8) used oral or IV doses ranging from 1mg daily to 250mg twice daily, usually for short durations (<6 months). Adverse events in these trials were generally rare (<10% of participants) and non-serious, and included gastrointestinal discomfort, nausea, vertigo, headache, flushing, rash, anxiety, drowsiness and dry mouth. Some but not all studies reported a transient drop in blood pressure with treatment (8). We found three possible serious adverse events association with Vinpocetine. A patient receiving 15mg daily for stroke developed agranulocytosis (a serious and potentially life-threatening abnormality in white blood cell count); no other cause for this was found and it resolved with G-CSF (which stimulates blood cell production) and discontinuation of Vinpocetine (50). Two patients receiving 5mg three times daily for mild cognitive impairment experienced "acute respiratory disease" (51).

Based on this side effect profile, ALSUntangled assigns a "Risks" grade of "D" (Table 1).

At a dose of 10mg twice daily, the cost of Vinpocetine is $8 per month (52). Unfortunately, as with many supplements, the labeled amount of Vinpocetine in different brands is often inaccurate when independently tested (53).

Conclusions

Vinpocetine has several plausible mechanisms by which it could slow ALS progression. There are two PALS online who reported improved motor functions on supplement cocktails containing Vinpocetine, but many other PALS have had no benefits. Serious side effects from Vinpocetine are rare and it is inexpensive. We support further study of Vinpocetine in ALS, but our group was split on what the next step should be; some were in favor of a study in a pre-clinical ALS model and others were in favor of a small human trial to confirm its benefit on cramps (7) and to explore whether it is safe, tolerable and might slow disease progression.

Disclosures of interest

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