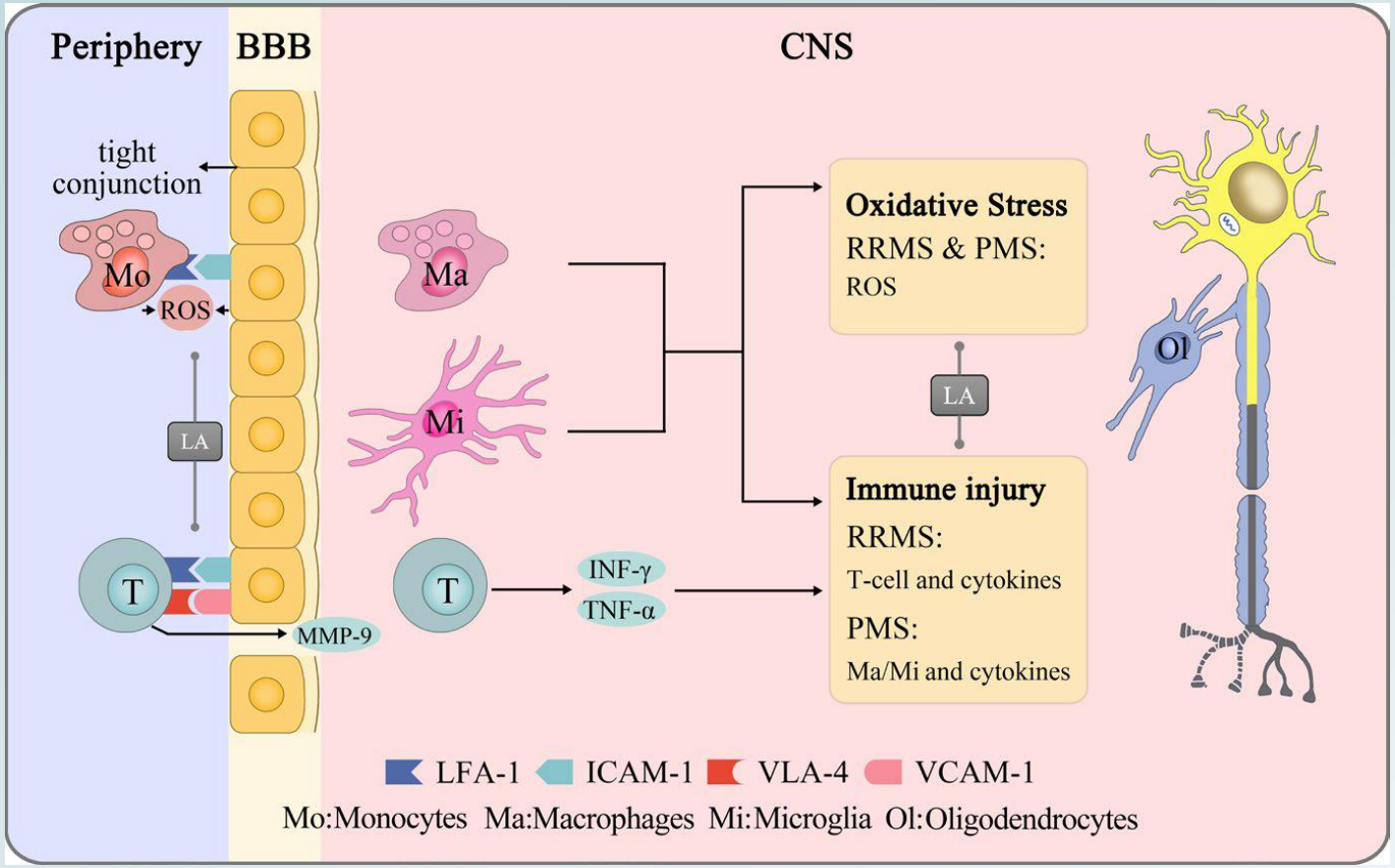
Mechanisms of Action of Lipoic Acid in MS

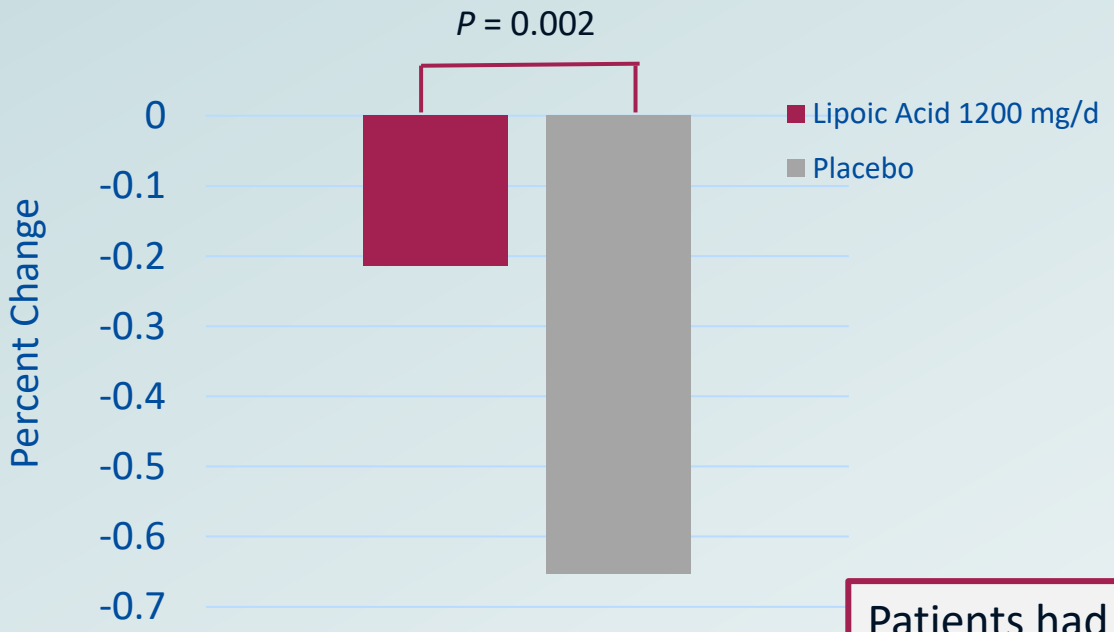


- Antioxidant, sold over-the-counter
- Lipoic acid reduces
  - Oxidative stress (periphery and CNS)
  - T-cell adhesion to brain endothelium
  - T-cell mediated penetration of BBB by inflammatory agents
  - Microglia and macrophage activity (CNS)

BBB, blood brain barrier; CNS, central nervous system; LA, lipoic acid; PMS, progressive multiple sclerosis; ROS, reactive oxygen species; RRMS, relapsing-remitting multiple sclerosis.
Xie H et al. *CNS Neurosci Ther*. 2022;28:319-331. (CC BY 4.0).

Lipoic Acid in 2 Year Phase 2 Trial in nSPMS

Primary Endpoint: Change in brain volume from baseline



Secondary Endpoints

- No significant difference between nSPMS groups for any other MRI measurements
- No significant between-group differences for any clinical outcomes
- Two secondary endpoints showed borderline significance
  - T2 lesion volume: *P* = 0.058
  - 25-foot walk time: *P* = 0.060
  - Small population sizes. For efficacy analysis,
    - Lipoic acid group: N = 26
    - Placebo group: N = 24

Patients had option to take glatiramer acetate or β-interferon. There were 11 subjects in each group taking DMT.

DMT, disease-modifying therapy; nSPMS, nonactive secondary progressive multiple sclerosis.

Spain R et al. *Neurol Neuroimmunol Neuroinflamm*.2017;4:e374.

Safety Analysis for Lipoic Acid in nSPMS

Safety Analysis	
Serious adverse events	• Six in each group • Only 1 in lipoic acid group considered treatment-related: vomiting and dehydration leading to hospitalization
Discontinuation	• Only in lipoic acid group • One patient each: MRI claustrophobia, nausea and vomiting, prostrate cancer, proteinuria (glomerulonephritis), renal failure
Gastrointestinal upset	More common in lipoic acid group than placebo (58% vs 7%, respectively; *P* = 0.007)
Falls	Less common in lipoic acid group than placebo (50% vs 96%, respectively; *P* = 0.03)
Renal function	2 patients who discontinued due to renal dysfunction Consulting nephrologist deemed cases likely not related to treatment Renal monitoring should be included in future studies of lipoic acid

nSPMS, nonactive secondary progressive multiple sclerosis.

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