

Memantine May Improve "Lupus Brain Fog" in SLE, Suggests Trial

USA: A small randomized, placebo-controlled trial has found that memantine modestly improved cognitive function in people with [systemic lupus erythematosus \(SLE\)](#) and [neuropsychiatric symptoms](#) after 12 weeks. The drug targets [NMDA receptors](#), which may be involved in SLE-related cognitive dysfunction. The findings suggest memantine may have potential for treating lupus-associated [cognitive impairment](#), but larger trials are needed to confirm its effectiveness.

The phase 2 ClearMEMory trial, published in the *Annals of the Rheumatic Diseases*, evaluated whether memantine could improve neuropsychological function in adults with SLE who had objectively documented cognitive dysfunction. The multisite study randomly assigned participants to receive memantine or placebo for 12 weeks, with the memantine dose gradually increased to a maximum of 40 mg/day.

The researchers assessed cognitive performance using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The primary outcome was the change in the total RBANS score from baseline to week 12. The study also examined the proportion of participants achieving a clinically meaningful improvement, defined as an increase of at least 8 points, along with participants' own perceptions of improvement.

Among 131 individuals screened, 56 were randomized, while 43 completed the primary outcome assessment and were included in the analysis. Of these, 18 received memantine and 25 received placebo.

The trial revealed the following findings:

- At 12 weeks, memantine produced greater improvement in overall cognitive function, with a median RBANS score increase of 8 points versus 5 points with placebo.
- A clinically meaningful improvement of ≥ 8 points in RBANS was achieved by 66.7% of participants receiving memantine versus 36.0% receiving placebo.
- The number needed to treat (NNT) was 3.3, suggesting that treating approximately 3–4 patients with memantine could result in one additional patient achieving clinically meaningful cognitive improvement compared with placebo.
- Self-reported improvement was more common with memantine (61% vs 36% with placebo), although the difference was not statistically significant.
- Treatment discontinuation due to adverse events occurred at similar rates with memantine and placebo (19% vs 17%, respectively).
- Memantine doses of up to 40 mg/day were tolerated by many patients, although adverse effects may require treatment with lower doses in some individuals.

Cognitive dysfunction remains a significant unmet need in SLE, often persisting despite immunomodulatory treatment. NMDAR dysfunction and NMDAR-targeting antibodies have been implicated in neuropsychiatric SLE. However, recruitment challenges, including a COVID-19-related enrollment pause, led to early study termination and a smaller-than-planned sample.

The 12-week follow-up also limited assessment of long-term efficacy and durability, while early discontinuations prevented an intention-to-treat analysis and the small sample restricted evaluation of secondary outcomes. Overall, the findings provide proof-of-concept evidence that memantine may improve cognitive manifestations of neuropsychiatric SLE, supporting the need for larger, longer-term trials.

Reference:

Rhoads, J. P., Ahmad, L. N., Williams, J., Du, L., Littlejohn, E. A., Subash, M. G., Shirey-Rice, J. K., Pulley, J. M., Self, W. H., Collar, E. M., Annapureddy, N., Barnado, A., Jackson, J. C., & Crofford, L. J. (2026). Improvement in neuropsychological function with memantine treatment among patients with systemic lupus erythematosus: A phase 2 randomised placebo-controlled clinical trial. *Annals of the Rheumatic Diseases*. <https://doi.org/10.1016/j.ard.2026.07.015>

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