Rapid Eye Movement Sleep-Suppressing Antidepressant Use Is Associated With Enhanced Survival in Amyotrophic Lateral Sclerosis

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RATIONALE
Patients with weakened inspiratory muscles are vulnerable to sleep disordered breathing, most acutely during rapid eye movement (REM) sleep. Pharmacological suppression of REM sleep has been found to improve sleep disordered breathing and nocturnal hypoxemia in patients with Duchenne muscular dystrophy as well as in patients with restrictive chest wall disease and nocturnal hypoventilation. To our knowledge, this approach has not been investigated in amyotrophic lateral sclerosis (ALS), the most common form of motor neuron disease.
METHODS
We queried the TriNetX Research network (Cambridge, MA), which aggregates the electronic health record (EHR) and claims-derived data of over 132 million patients (primarily in the US) for patients diagnosed with ALS (ICD-10-CM G12.21) and prescribed riluzole (RxNorm 35623) between 09/2003 - 09/2023. We defined a REM-inhibited cohort in which patients were prescribed one of several antidepressant medications associated with the suppression of REM sleep in the 3 years preceding inclusion criteria, as well as a non-REM-inhibited cohort who received antidepressants not linked to REM suppression, excluding patients who received prescriptions from both classes. The primary outcome was 2-year survival, analyzed using Kaplan-Meier methodology with log-rank testing and hazard ratios estimated using Cox proportional hazards models. Propensity score matching was performed using age, race, and gender.
RESULTS
We identified 17,444 patients with ALS who met inclusion criteria, 2,492 (14.3%) of which made up the REM-inhibited cohort and 365 (2.1%), the non-REM-inhibited cohort. Two-year Kaplan-Meier survival was significantly higher in the REM-inhibited group prior to propensity score matching (47.18% vs 41.06%, log-rank p=0.027; Figure 1), with a hazard ratio of 1.21 (95% CI 1.022 - 1.433). This survival benefit trend persisted but did not reach significance after matching (48.13% vs 41.06%, log-rank p=0.072; HR 1.23, 95% CI 0.981 - 1.547). Preserved proportionality (p=0.442) suggested a consistent treatment effect throughout follow-up.
CONCLUSION
To our knowledge, this is the first study examining differential survival in ALS patients receiving REM-inhibiting versus non-REM-inhibiting antidepressants. The observed survival benefit aligns with findings from other neuromuscular disorders, where REM sleep suppression ameliorates nocturnal respiratory dysfunction. While our investigation was limited by its retrospective nature and potential confounding factors inherent to EHR data, the results suggest that pharmacologically targeting a period of known vulnerability in ALS may have meaningful clinical impact. These findings justify prospective trials of REM-targeted interventions, particularly given the limited treatment options currently available for ALS.

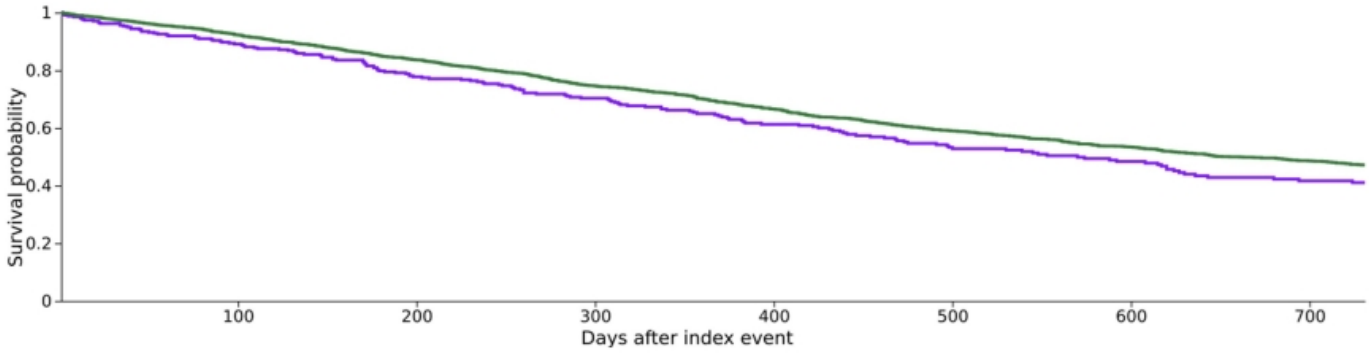

Figure 1. Kaplan – Meier survival analysis at 2 years from index criteria (the presence of ALS diagnosis with riluzole), with the REM-inhibited cohort exhibiting a survival probability of 47.18% (green) and the non-REM-inhibited cohort, 41.06% (purple); log-rank p=0.027.

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