



Understanding Treatment Barriers and Adherence Among People Living with Amyotrophic Lateral Sclerosis in Real World Clinical Practice

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BACKGROUND

- Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with only three approved treatments in North America: Riluzole, edaravone, tofersen.
 - Please note, in March 2024, the results of the PHOENIX Phase 3 trial were released showing that sodium phenylbutyrate (PB) and taurursodiol/ursodoxicoltaurine (TURSO) failed to meet its primary endpoint in ALS. Thus, PB and TURSO is being removed from the market.
- Poor treatment adherence reduces clinical effectiveness which can adversely impact disease progression and mortality rates (Introna et al., 2018).
- Understanding barriers and adherence to treatment in real world clinical practice is essential to address these issues.
- The objective of the current study was to perform a scoping review to identify knowledge gaps on the incidence of non-adherence and barriers to ALS treatment in clinical practice using real world data (RWD).

METHODS

- This scoping review was conducted in February 2024 before the results of the PHOENIX trial were released and as such, PB and TURSO was included in the search terms.
- The scoping review proposed the following two questions and search terms:

Q1. To describe the incidence of non-adherence to ALS drugs in the real world

Example Search Terms

- Treatment and adherence and amyotrophic lateral sclerosis*
- Medication and adherence and amyotrophic lateral sclerosis
- Adherence and amyotrophic lateral sclerosis
- Compliance and amyotrophic lateral sclerosis
- Treatment and compliance and amyotrophic lateral sclerosis*
- Treatment and amyotrophic lateral sclerosis*
- Treatment and ALS and adherence and real-world data*
- Treatment and ALS and compliance and real-world data*

Q2. What are the known barriers associated with low adherence to ALS treatments in the real world?

Example Search Terms

- Barriers and treatment and adherence and amyotrophic lateral sclerosis*
- Barriers and medication and adherence and amyotrophic lateral sclerosis
- Barriers and amyotrophic lateral sclerosis
- Barriers and treatment and compliance and amyotrophic lateral sclerosis*
- Barriers and treatment and amyotrophic lateral sclerosis*
- Treatment and ALS and barriers and real-world data*

*PB and TURSO, riluzole, edaravone, and tofersen were the only ALS treatments entered into the search. For the full list of search terms please click this link.

Search Details

Inclusion Criteria

- Published in English.
- Included adults with a diagnosis of ALS.
- Explored treatment non-adherence in ALS in real world clinical practice, and/or identified possible barriers associated with non-adherence in real world clinical practice.
- Focused on ≥1 of the four approved ALS medications (PB and TURSO, riluzole, edaravone, or tofersen).
- Used a measurement of adherence.

Types of Studies Included

- Case reports
- Observational study
- Real-world data

Types of Studies Excluded

- Books
- Documents
- Comments
- Clinical trials
- Editorials
- Reviews

Additional Filters

- Human
- Adults 19yrs+

Databases Searched

- PubMed
- Medline
- Google Scholar

Search Strategy

- An initial search of PubMed was conducted to identify text words contained in the title, abstract and keywords that could be used as alternative search terms.
- A more detailed search was then undertaken using identified search terms across the databases.
- The reference list of identified studies were manually searched for additional studies.

Study Selection

- Study selection was performed by all authors, against inclusion criteria in 2 stages.
 - Stage 1: Title and abstract review
 - Stage 2: Full text review (if required)

RESULTS

- A total of 10 studies were retrieved that met the inclusion criteria for Q1 (Figure 1).
 - 5 studies were conducted in Italy, 3 in the USA, 1 in Portugal, and 1 in Japan.
 - 7 assessed riluzole and 3 assessed edaravone. No studies assessed PB and TURSO or tofersen.
- No studies met the inclusion criteria for Q2 (Barriers as the primary outcome) (Figure 2).

FIGURE 1. Flow Chart Of Study Selection For Q1

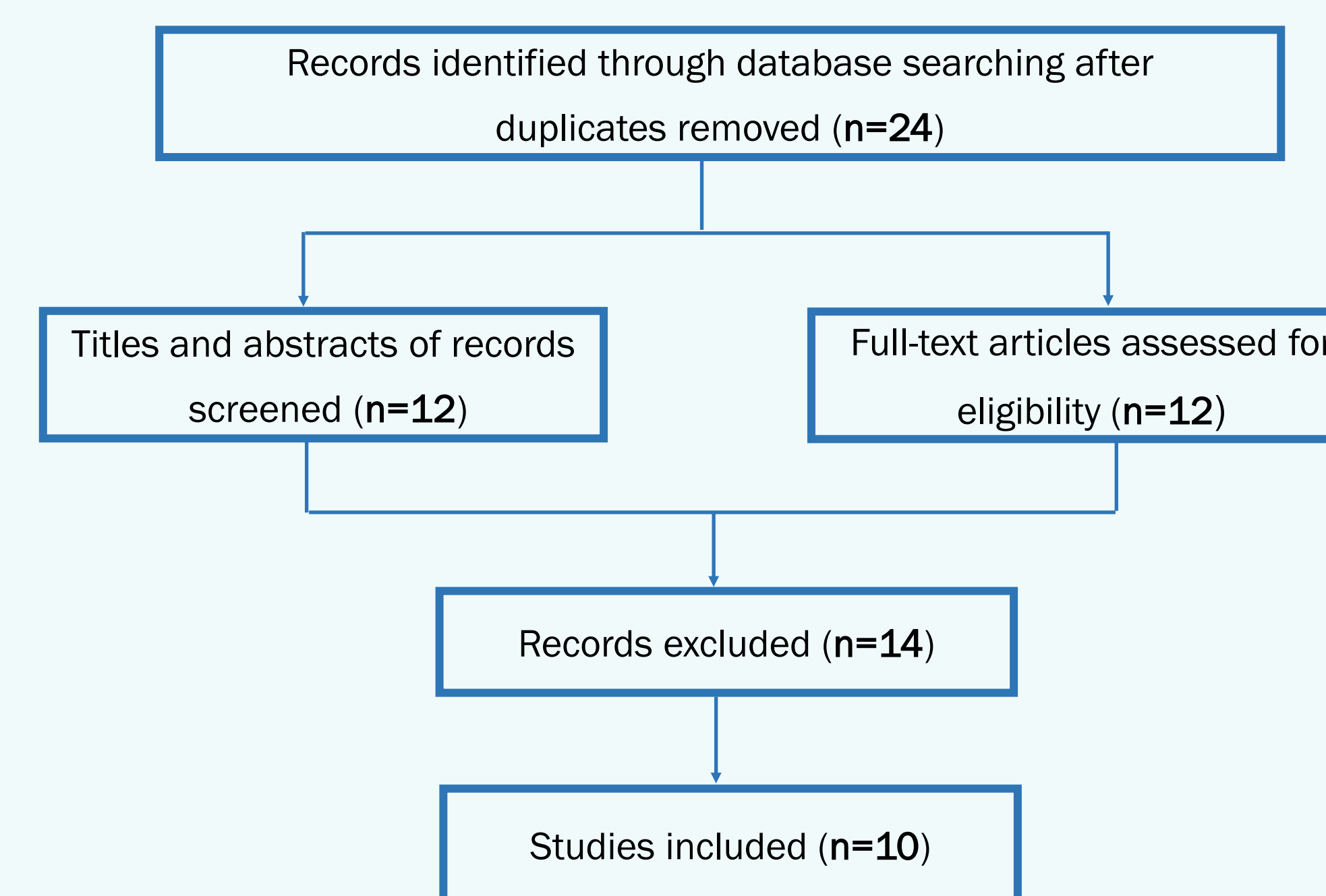
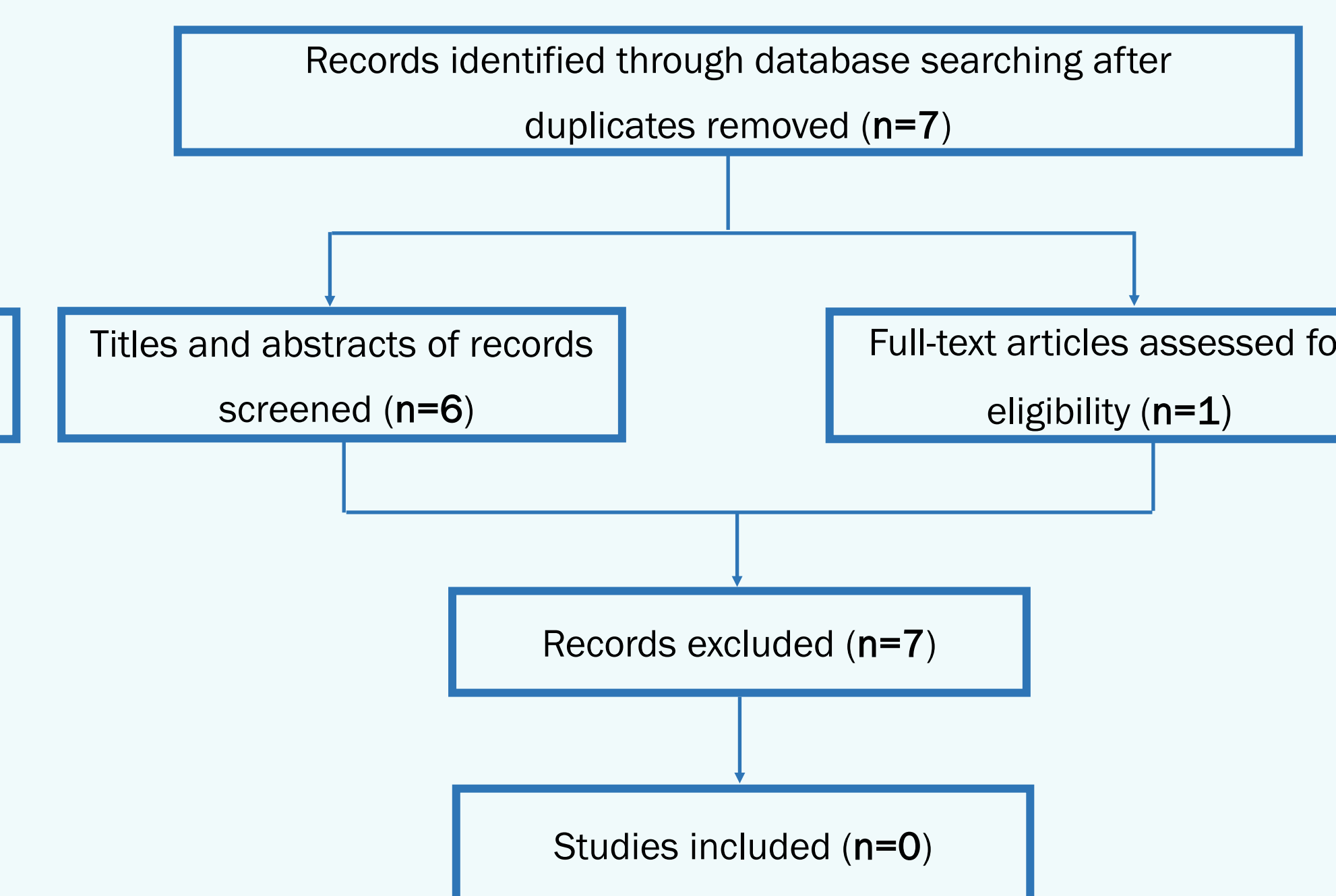


FIGURE 2. Flow Chart Of Study Selection For Q2



- The Table below highlights the key findings:

| Article | Data | N | Treatment | Discontinuations / adherence data | Factors associated with low adherence |
|----------------------|--|--------|-----------|---|---|
| Chio et al. 2002 | Italian registry 1995-1996 | 119 | Riluzole | 5 patients discontinued after 3wks | Nausea |
| Fortuna et al. 2019 | Italian registry 2017-2018 | 31 | Riluzole | 7 patients discontinued after <6mths | DVT, acute lung injury, lack of efficacy |
| Geronimo et al. 2022 | USA retrospective chart review 2007-2016 | 508 | Riluzole | 83% receiving percutaneous endoscopic gastrostomy persisted | Abnormal AST/ALT, GI side effects, cost, patient preference, advanced disease |
| Gilbert et al. 2019 | USA registry 2012-2017 | 28,646 | Riluzole | 46% getting a tracheostomy persisted 40% highly adherent 8% moderately adherent | Not reported |
| Giometto et al. 2024 | Italian registry 2014-2019 | 671 | Riluzole | High adherers had values of 80 to >90% Others had adherence of 50% at 4mths and 20% at 1yr | CNS comorbidity, respiratory and CVD, no use of nonpharmacological treatments |
| Introna et al. 2018 | Italian registry 2016-2017 | 45 | Riluzole | Not reported | Side effects, dysphagia |
| Parola et al. 2018 | Portugal retrospective study 2006-2016 | 77 | Riluzole | Mean adherence was 91.2% | GI intolerance, lack of efficacy |
| Lunetta et al. 2020 | Italian observational study 2017-2019 | 331 | Edaravone | 22 patients suspended treatment after 6mths | Lack of efficacy, treatment burden |
| Okada et al. 2019 | Japan registry 2010-2016 | 27 | Edaravone | 10 patients discontinued | Renal dysfunction, vein inflammation, pneumonia, lack of vascular access |
| Vu et al. 2020 | USA registry 2017-2019 | 369 | Edaravone | 59.9% discontinued | Not reported |

Abbreviations: ALT, Alanine transaminase; AST, Aspartate transferase; CNS, central nervous system; CVD, cardiovascular disease; DVT, deep vein thrombosis; GI, gastrointestinal; mths, months; wks, weeks; yr, year.

DISCUSSION and CONCLUSION

- Available studies primarily focused on riluzole and estimates for non-adherence/non-persistence were highly variable, e.g., Chio et al., 2002 reported low levels of adherence at 4.2%; whilst Geronimo et al., 2022 and Gilbert et al., 2019 reported moderate levels of adherence at 17%-54% and 52%, respectively.
- Other studies reported very high discontinuation rates between 37%-59.9% (Okada et al., 2019; Vu et al., 2020).
- Persistence measurement is likely confounded by stage of disease and measurement differences making it challenging to interpret the magnitude of the problem with existing data.
- Similarly, reported barriers to adherence were highly variable – mostly focused on adverse health events that may or may not have been related to the ALS treatment.
- These findings demonstrate a clear need for further study to determine the extent to which negative patient outcomes could be delayed with improved drug use.
- Finally, there is a clear need for guidance to help standardize measurement approaches for non-adherence in the ALS population and identify direct causes.

- The scoping review proposed the following two questions and search terms:
 1. To describe the incidence of non-adherence to ALS drugs in the real world.

| Search Terms | |
|--|---|
| 1. Treatment and adherence and amyotrophic lateral sclerosis | 11. Tofersen and amyotrophic lateral sclerosis |
| 2. Medication and adherence and amyotrophic lateral sclerosis | 12. PB and TURSO and amyotrophic lateral sclerosis and adherence and real-world data |
| 3. Adherence and amyotrophic lateral sclerosis | 13. Riluzole and amyotrophic lateral sclerosis and adherence and real-world data |
| 4. Compliance and amyotrophic lateral sclerosis | 14. Edaravone and amyotrophic lateral sclerosis and adherence and real-world data |
| 5. PB and TURSO and adherence and amyotrophic lateral sclerosis | 15. Tofersen and amyotrophic lateral sclerosis and adherence and real-world data |
| 6. PB and TURSO and compliance and amyotrophic lateral sclerosis | 16. PB and TURSO and amyotrophic lateral sclerosis and compliance and real-world data |
| 7. Riluzole and adherence and amyotrophic lateral sclerosis | 17. Riluzole and amyotrophic lateral sclerosis and compliance and real-world data |
| 8. Riluzole and compliance and amyotrophic lateral sclerosis | 18. Edaravone and amyotrophic lateral sclerosis and compliance and real-world data |
| 9. Edaravone and adherence and amyotrophic lateral sclerosis | 19. Tofersen and amyotrophic lateral sclerosis and compliance and real-world data |
| 10. Edaravone and compliance and amyotrophic lateral sclerosis | |

2. What are the known barriers/factors associated with low adherence to ALS treatments in the real world?

| Search Terms | |
|---|---|
| 1. Barriers and adherence and amyotrophic lateral sclerosis and treatment | 8. Barriers and Edaravone and adherence and amyotrophic lateral sclerosis |
| 2. Barriers and medication and adherence and amyotrophic lateral sclerosis | 9. Barriers and Edaravone and compliance and amyotrophic lateral sclerosis |
| 3. Barriers and amyotrophic lateral sclerosis | 10. Barriers and Tofersen and amyotrophic lateral sclerosis |
| 4. Barriers and PB and TURSO and adherence and amyotrophic lateral sclerosis | 11. PB and TURSO and amyotrophic lateral sclerosis and barriers and real-world data |
| 5. Barriers and PB and TURSO and compliance and amyotrophic lateral sclerosis | 12. Riluzole and amyotrophic lateral sclerosis and barriers and real-world data |
| 6. Barriers and Riluzole and adherence and amyotrophic lateral sclerosis | 13. Edaravone and amyotrophic lateral sclerosis and barriers and real-world data |
| 7. Barriers and Riluzole and compliance and amyotrophic lateral sclerosis | 14. Tofersen and amyotrophic lateral sclerosis and barriers and real-world data |

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- Dr David Blackburn does not report any conflict of interest.
- Diana Bolano Del Vecchio, is an employee of Amylyx Pharmaceuticals. As a full-time employee of Amylyx Pharmaceuticals, she may have stock option ownership in Amylyx Pharmaceuticals, Inc.