TROFINETIDE FOR RETT SYNDROME: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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INTRODUCTION

Rett syndrome is a debilitating neurodevelopmental disorder primarily affecting females, characterized by a period of normal development followed by regression of acquired skills, typically between 6 and 18 months of age.

OBJECTIVES

This systematic review and meta-analysis aims to provide an updated assessment of the efficacy and safety of trofinetide in the treatment of Rett syndrome, based on evidence from randomized controlled trials.

METHODOLOGY

We systematically searched the EMBASE, PubMed, and Cochrane databases to identify randomized controlled trials comparing trofinetide versus placebo in patients with RS for a duration of 12 weeks. The primary outcome measures evaluated were the scores on the Rett Syndrome Behaviour Questionnaire (RSBQ) and Clinical Global Impression scale (CGI-I), as well as adverse events. Heterogeneity was assessed using I^2 analysis, and all statistical analyses were performed using R software version 4.3.2 and a random-effects model.

Results/Discussion

Meta-analysis:

- Included 4 RCTs with a total of 448 patients with Rett syndrome.

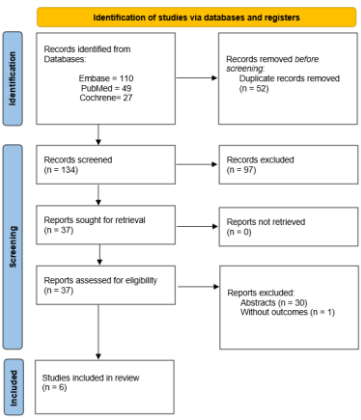
Efficacy of trofinetide:

- RSBQ: significant improvement (MD 2.78; 95% CI 1.20–4.3; $p < 0.0001$; $I^2 = 97.5\%$).
- CGI-I: significant improvement (MD 0.27; 95% CI 0.09–0.45; $p < 0.0001$; $I^2 = 98.7\%$).

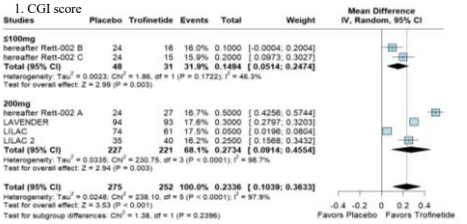
These findings suggest a positive impact on both behavioral outcomes and overall clinical status.

Safety (adverse events):

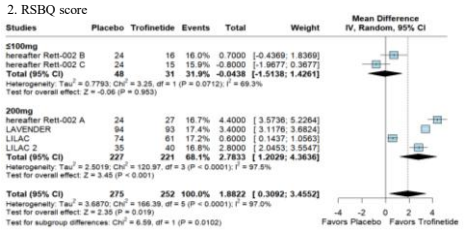
- Diarrhea: higher incidence (RR 2.50; 95% CI 0.72–8.67; $p < 0.0001$; $I^2 = 96.8\%$).
- Vomiting: no significant difference (RR 1.10; 95% CI 0.48–2.52; $p > 0.01$; $I^2 = 81\%$).
- Pyrexia: no significant difference (RR 1.31; 95% CI 0.79–2.18; $p = 0.5965$; $I^2 = 0\%$).
- Irritability: trend toward increase, but not significant (RR 3.36; 95% CI 0.93–12.1; $p = 0.3677$; $I^2 = 0.1\%$).



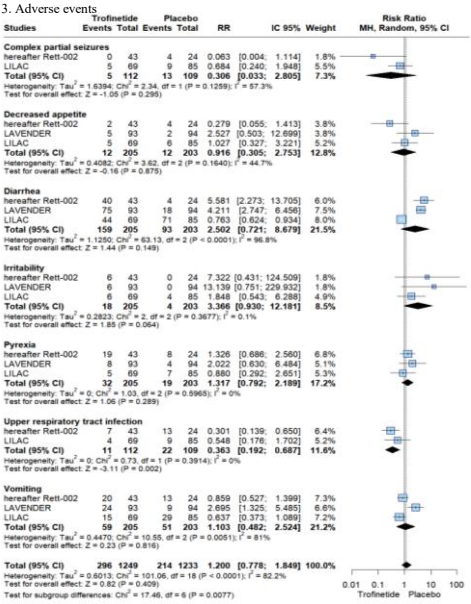
1. CGI score



2. RSBQ score



3. Adverse events



CONCLUSION

- **Trofinetide significantly improves core symptoms of Rett syndrome (RSBQ, CGI-I).**
- **Adverse events are more frequent but not statistically significant and generally manageable.**
- **Further studies are needed to clarify long-term and age-related effects.**

REFERENCES

Petriti U, et al. Global prevalence of Rett syndrome: systematic review and meta-analysis. Syst Rev. 2023;12(1):5. doi:10.1186/s13643-023-02169-6

Youakim J, Barrett A, Neul JL, Percy AK, Benke TA, Berry-Kravis EM, et al. Trofinetide for the treatment of Rett syndrome: Long-term safety and efficacy in the LILAC-2 open-label extension study. Med. 2024. doi:10.1016/j.medj.2024.06.007

Percy AK, Ryther R, Marsh ED, Neul JL, Benke TA, Berry-Kravis EM, et al. Results from the phase 2/3 DAFFODIL study of trofinetide in girls aged 2-4 years with Rett syndrome. Med. 2025;6(6):100608. doi:10.1016/j.medj.2025.100608

Percy AK, et al. Treatment with trofinetide for ≤40 weeks continued to improve symptoms of Rett syndrome: Results from the open-label extension LILAC study. Med. 2024;5(9):1178-1189.e3. doi:10.1016/j.medj.2024.05.018

Marsh ED, Neul JL, Benke TA, Berry-Kravis EM, Percy AK, Barrett A, et al. Trofinetide for the treatment of Rett syndrome: Phase 3, randomized, double-blind, placebo-controlled LAVENDER study. Med. 2023.

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