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Clinical, humanistic, and economic burden of Rett syndrome: A systematic review

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INTRODUCTION

- Rett syndrome is a rare, progressive, and severe neurodevelopmental disorder that primarily affects females, with an estimated prevalence of 1 in 10,000 live female births (Orphanet 2021). It is caused by mutations in the *MECP2* gene on the X chromosome (Kyle 2018).
- The disease typically manifests between 6 and 18 months of age, and although symptoms vary considerably among affected individuals, it is characterized by significant cognitive and physical impairments, loss of purposeful hand skills, autistic-like behaviors, and loss of communication skills (Kyle 2018).
- Caregivers of individuals with Rett syndrome face significant challenges that affect their quality of life (QoL) across physical health, mental health, and social interactions (Larsen 2024).
- This systematic literature review (SLR) assessed the clinical efficacy, effectiveness, and safety of interventions for Rett syndrome and examined the humanistic and economic burden associated with Rett syndrome.

METHODS

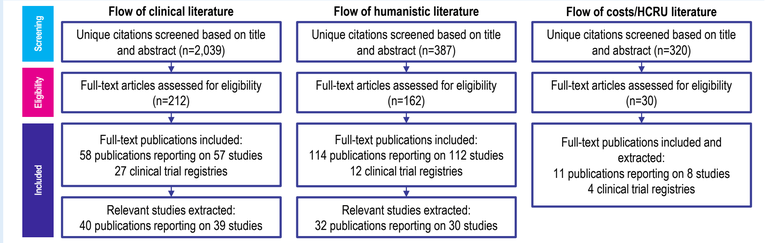
- The SLR search was conducted using the following databases: Embase, Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, National Health Service Economic Evaluation Database, EconLit, and Database of Abstracts of Reviews of Effects from database inception through 8 June 2023.
- Recent congress proceedings (2021-2023), clinical trial registries (clinicaltrials.gov, clinicaltrialsregister.eu), International Clinical Trials Registry Platform, Health Canada's Clinical Trials Database (database inception until June 2023), and reference lists from other SLRs published between 2018 and 2023 were also reviewed.
- Titles/abstracts and full-text publications were independently screened by 2 researchers to include observational or interventional studies reporting on Rett syndrome patients aged ≥2 years that reported on the efficacy and safety of any pharmacological interventions, humanistic burden, economic burden (cost/healthcare resource use [HCRU]), or pharmacoeconomic evaluations. For screening disagreements, a final determination was made by a third independent researcher.
- Full data extraction was conducted by one researcher, with full validation by a second, independent researcher. For the clinical and humanistic reviews, data extraction was completed for relevant studies defined as clinical studies evaluating treatment effect as the primary objective and humanistic studies reporting utility values, lost work productivity due to caregiving, or validated QoL measures.
- Risk of bias assessment was conducted following the recommendations provided by the Centre for Research and Dissemination Guidance for Reviews and the Cochrane Handbook for Systematic Reviews of Interventions.

RESULTS

Data were extracted from relevant publications reporting on clinical (n=40), humanistic (n=32), and cost/HCRU (n=11) outcomes (**Figure 1**). There were 221 unique citations screened for pharmacoeconomic models, but no publications on this topic were eligible for inclusion in the SLR.

- Less than half of the clinical studies were randomized controlled trials (RCTs), and most studies across all topics had small sample sizes. Enrolled individuals tended to be from high-income countries, female, and children or adolescents. Most included studies had a low to moderate risk of bias.
- Primary endpoints were specified in 7 clinical trials (3 RCTs, 1 crossover RCT, 3 single-arm trials) of 5 interventions designed to assess the treatment effect on clinical severity or other key components of Rett syndrome (**Table 1**). Of these, only 2 trials were placebo-controlled. Results from these trials are summarized below and ordered from more to less favorable clinical outcomes for the treatment being assessed.
  - Trofinetide led to significant improvement of the coprimary endpoints vs placebo.
  - Some doses of dextromethorphan polistirex led to a significant improvement in some clinical outcomes vs other doses and between baseline and follow-up, although the primary endpoint was not met.
  - There were no significant changes in clinical outcomes at follow-up vs baseline after treatment with fingolimod.
  - Mixed findings were reported at follow-up timepoints vs baseline, including life-threatening safety concerns, with glatiramer acetate.
  - Mecasermin was associated with symptom worsening vs placebo.
- Measures used to evaluate QoL varied. The Quality of Life Inventory-Disability scale was relatively commonly used to assess QoL in individuals with Rett syndrome (6 out of 30 studies [20%]). The independence domain was consistently the lowest-scoring domain, while social interactions and positive emotions were the highest-scoring domains (**Figure 2**).
- Functional impairments caused by Rett syndrome necessitated intensive 24-hour caregiving, particularly for activities of daily living. This requirement placed a significant mental and emotional burden on caregivers, as supported by the psychological and social outcomes observed among them (**Figure 3**). Most caregivers reported using some type of respite service to manage this responsibility (**Figure 4**).
- The burden on caregivers was further highlighted by the HCRU associated with Rett syndrome. Individuals with this condition often required multiple therapies and specialized devices, the coordination of which fell to the caregiver (**Figure 4**).
- Limited cost data were available in the literature, but where comparative data were reported, healthcare costs associated with Rett syndrome were higher than healthcare costs for the general population. Residential care, home/hospice care visits, therapeutic services, and outpatient and inpatient visits were the main cost drivers.

Figure 1. Flowchart for selection of studies in the SLR



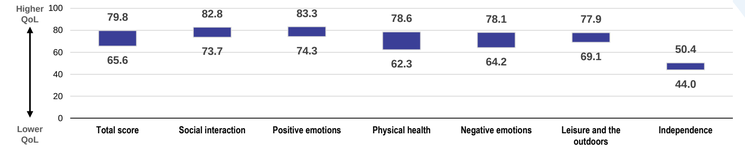
PRISMA flow of literature diagrams for clinical, humanistic, and costs/HCRU outcomes. All publications meeting PICOS criteria were included. Data extraction was completed for relevant publications, which were defined as clinical studies evaluating treatment effect as the primary objective and humanistic studies that reported utility values, lost work productivity due to caregiving, or validated QoL measures.
Key: HCRU – healthcare resource use; PICOS – population, interventions, comparators, outcomes, study design; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QoL – quality of life; SLR – systematic literature review.

Table 1. Results from studies designed to assess treatment effect on clinical severity or other components of Rett syndrome with a specified primary endpoint

Trial	Intervention vs comparator	Study design (trial phase)	N	Primary endpoints	Primary results reported by authors	Clinical findings[a]
Smith-Hicks 2017	Dextromethorphan polistirex 0.25 mg/kg/day vs 2.5 mg/kg/day vs 5.0 mg/kg/day and vs baseline	RCT (phase 2)	38	Spike activity	There was no difference in the distribution of spike counts across doses for either visit 1 or 2 and no significant changes in spike count between the 2 visits for each dose	Significantly improved cognition/communication/psychosocial outcomes
Naegelin 2021	Fingolimod vs baseline	Single-arm trial (phase 1/2)	6	Efficacy: Change in levels of BDNF in serum/CSF and change in deep gray matter volumes (thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens) measured by MRI Safety: White blood cell/lymphocyte counts, liver enzymes, and occurrence of any (serious) adverse events	Primary outcome measures were not met	No significant changes
Djukic 2016	Glatiramer acetate vs baseline	Single-arm trial (phase 2)	10	Gait velocity	Gait velocity improved significantly from baseline	Significantly improved ADLs and cognition/communication/psychosocial outcomes
Nissenkorn 2017	Glatiramer acetate (no comparator)	Single-arm trial (phase 2)	14	Safety and tolerability of the treatment and decrease in epileptiform activity as recorded in a 24-hour electroencephalograph	Terminated due to life-threatening safety concerns; prespecified outcomes not assessed	
O'Leary 2018	Mecasermin vs placebo	Crossover RCT (phase 2)	30	ADAMS Social Avoidance subscale, RSBQ Fear/Anxiety subscale, PTSVAS top 3 concerns, CGI-EI, PGI-EI, and the Kerr (overall) severity scale	Kerr severity scale, ADAMS Depressed Mood subscale, Visual Analog Scale Hyperventilation, and delta average power change scores significantly increased, implying worsening of symptoms	Significantly worse Rett-specific global function and cognition/communication/psychosocial outcomes
Glaze 2019	Trofinetide vs placebo	RCT (phase 2)	82	Safety and PK	No significance testing reported; "All dose levels were well tolerated and generally safe"	Significantly improved Rett-specific global function and general global function
Neul 2023	Trofinetide vs placebo	RCT (phase 3)	187	Coprimary endpoints: RSBQ total score (change from baseline to week 12 and CGI-I score at week 12)	Significant improvement for both coprimary endpoints	Significantly improved Rett-specific global function, general global function, and cognition/communication/psychosocial outcomes

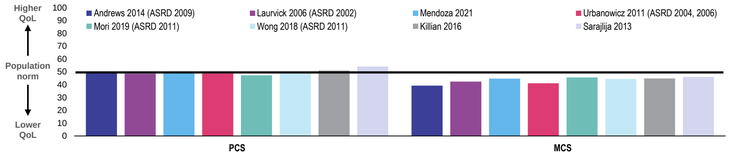
[a] Clinical findings summarize primary outcomes and other clinical outcomes, including Rett-specific function, general global function, ADLs, and cognition/communication/psychosocial outcomes.
Key: ADAMS – Anxiety, Depression, and Mood Scale; ADL – activities of daily living; BDNF – brain-derived neurotrophic factor; CGI-EI – Clinical Global Impressions-Efficacy Index; CGI-I – Clinical Global Impressions-Improvement; CSF – cerebrospinal fluid; MRI – magnetic resonance imaging; PGI-EI – Parent Global Impression-Efficacy Index; PK – pharmacokinetics; PTSVAS – Parent-Targeted Symptoms Visual Analog Scale; RSBQ – Rett Syndrome Behavior Questionnaire.
Purple – Significant benefit for intervention assessed compared to control/placebo or baseline; Grey – No significant differences for treatment compared to control/placebo or baseline; Pink – Significantly worse results for the intervention assessed compared to control/placebo or baseline; **No shading** – Significance not assessed.

Figure 2. Quality of Life Inventory-Disability score ranges across included trials



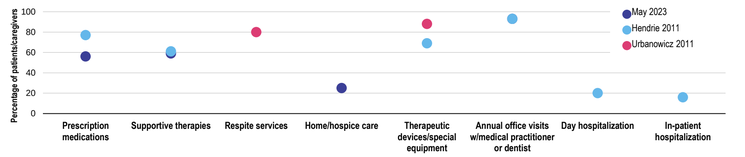
Key: QoL – quality of life.
Data from Downs 2019, Downs 2023, Leonard 2022, Mendoza 2021, Stahlhut 2020, and Williams 2021.

Figure 3. Caregiver QoL from the SF-36/SF-12 in reference to the population norm



Key: ASRD – Australian Rett Syndrome Database; MCS – mental component summary; PCS – physical component summary; SF-12 – 12-Item Short Form Health Survey Questionnaire; SF-36 – 36-Item Short Form Health Survey Questionnaire; QoL – quality of life.

Figure 4. Healthcare resource use for individuals with Rett syndrome



CONCLUSION

- Rett syndrome is a devastating condition associated with significant challenges, including limited functional abilities for those affected, strain on the healthcare system due to considerable HCRU, costs from specialty services and equipment, and substantial caregiver burden.
- Globally, there is an urgent need for effective treatments. Currently, symptomatic care remains the only option outside of the US. Trofinetide, approved in the US in March 2023, stands as a significant advancement in this field and is the only therapy approved for Rett syndrome in the US or globally.
- Improvement in clinical outcomes may lead to improvements in patient and caregiver QoL (Bishop 2023). However, better clinical outcomes do not always equate to lower costs or reduced HCRU. Evaluations should therefore include the following humanistic outcomes: patient experiences and caregiver perspectives.
- Notably, research gaps exist. The lack of male participants in clinical studies raises questions about treatment efficacy for boys and men with Rett syndrome. Most evidence focuses on younger patients, even though individuals with Rett syndrome live into adulthood. Furthermore, the absence of pharmacoeconomic models and comprehensive estimates of the total economic burden is noteworthy. Filling these gaps will enhance our understanding of Rett syndrome's impact on patients, caregivers, and healthcare systems.

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