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Application of causal inference to identify determinants of seizure reduction and quality of life in patients with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC) treated with cannabidiol (CBD)

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Teresa Greco
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Teresa Greco is a passionate and enthusiastic biostatistician, inspired by great leaders from whom she seeks to learn qualities of vision, authenticity, vulnerability, resilience and persuasion. She holds a PhD in Biomedical Statistics from the University of Milan and a Master of Statistics Science from the University of Milan-Bicocca. She has 15 years of experience in clinical trials and statistical analysis gained in both research institutes and industry.
Teresa is the first author or co-author of 40 scientific papers. Her recent research focuses on the application in clinical trial settings of innovative statistical methods such as Bayesian networks and causal inference.
In her recent publication [1], the Bayesian network theory was reviewed and applied to a clinical case study, presenting an analytical approach to investigating and visualising causal relationships among key factors impacting adult patients with multiple sclerosis-related spasticity. The adherence score was proposed as a new metric to compare data networks' patterns based on different variables' discretisation.
The causal inference framework has been adopted to calculate the marginal average exposure effect through inverse probability weighting using the propensity score model, between changes in spasticity severity and improvements in spasticity-associated symptoms in patients with multiple sclerosis [2].
In the proposed abstract [3], the Structural Causal Model methodology (i.e., a combination of equations and graphs to delineate causal relationships [4]) has been applied to identify the system of structural functions assumed to be involved in the seizure reduction and quality of life improvement pathway in patients with Lennox-Gastaut syndrome, Dravet syndrome and tuberous sclerosis complex, treated with or without cannabidiol.
Teresa previously worked at the Anesthesiology and Cardiothoracic Surgery Department at San Raffaele Hospital and at QuintilesIMS srl, where she gained experience in the statistical analysis of clinical trials (phase I-IV, pre- and post-market approval), real-world studies (for regulatory, market, or scientific purposes), meta-analyses, network meta-analyses using both Bayesian and frequentist frameworks, standard/causal inference and scientific publication development. Recently, Teresa worked as Principal Biostatistician at LivaNova, where she helped to promote, explore, plan and execute applications in clinical and real-word device settings, complete clinical and market access and value requirements and coordinate regulatory activities.
Currently, Teresa is Associate Director of Medical Affairs Statistics at Jazz Pharmaceuticals. In this role, she manages and oversees multiple drug compound portfolios and leads biostatistics activities related to the design, analysis, and publication of results from phase IV, observational, and post-authorisation safety studies, as well as post hoc analyses and post-marketing commitments.

Teresa is a member of the Statisticians in the Pharmaceutical Industry society and the Società Italiana di Biometria (SIB) and is an active volunteer with The Effective Statistician organisation. She is committed to innovation and high performance, always striving for excellence.

[1] Greco T, Poole EM, Young AC, Alexander JK. Application of the Bayesian network theory in clinical trial data: Severity shift in spasticity numeric rating scale in patients with multiple sclerosis. Mult Scler Relat Disord. 2024;83:105466. 2024 Jan 21. PMID: 38310831.
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[3] Greco T, Boffa M, Specchio N, Auvin S. Application of causal inference to identify determinants of seizure reduction and quality of life in patients with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC) treated with cannabidiol (CBD). Proposed to Statisticians in the Pharmaceutical Industry (PSI) Conference 1–4 June 2025; London, (UK).
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Background:

Causal inference modelling investigates relationships between factors within populations. We analysed the relationship between seizure reduction and Caregiver Global Impression of Change (CGIC).

Methods:

Structural Causal Model (SCM) methodology was applied to data from patients with LGS, DS, or TSC from randomised controlled trials (RCTs) and open-label extension (OLE) studies investigating highly purified CBD (Epidyolex®[EU]/Epidiolex®[US]; 100 mg/mL oral solution). The primary objective was to confirm the causal-effect relationship between end-of-RCT (Weeks 14–16) seizure reduction and Week 24 (Wk24) CGIC as influenced by baseline characteristics, CBD treatment, comorbidities and adverse event number. Mediation analysis estimated direct/indirect effects impacting CGIC. *P*-values were uncontrolled for multiplicity.

Results:

Among 371 patients (138 LGS; 86 DS; 147 TSC), a significant causal-effect relationship between seizure reduction and CGIC was confirmed in patients with LGS or TSC ($P<0.05$; Figure 1), but not DS ($P>0.05$). Direct effects (± standard error) of CBD treatment on reducing end-of-RCT seizure frequency (−0.13±0.051, $P=0.008$), and of the latter on Wk24 CGIC (0.21±0.049, $P<0.0001$) were determined. Data confirmed an indirect effect of CBD treatment on Wk24 CGIC (−0.03±0.013, $P=0.03$), and a direct effect of number of comorbidities on Wk24 CGIC (−0.11±0.050, $P=0.03$) and Wk24 adverse events (0.15±0.051, p=0.0003). Seizure reduction and CGIC scores were unaffected by baseline characteristics.

Conclusions:

Analysis suggested a causal-effect relationship between CBD treatment, seizure reduction, and CGIC. SCM could be useful for defining nonseizure endpoints as key outcomes in future clinical trials.

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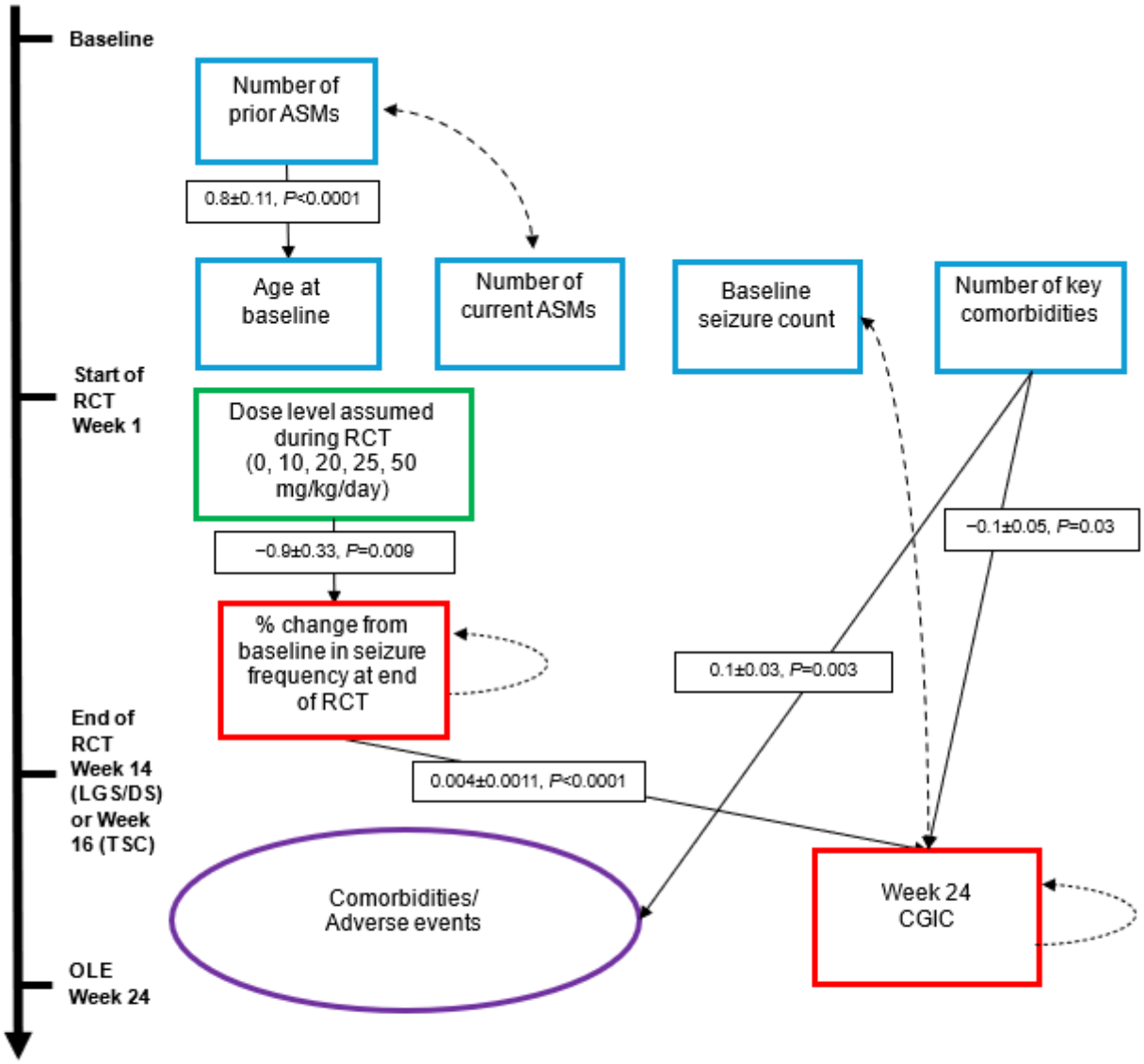
Figure 1. Path coefficient estimates in the final SCM



ASM, antiseizure medication; CGIC, Caregiver Global Impression of Change; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomised controlled trial; TSC, tuberous sclerosis complex.

Data are estimates ± standard error. Rectangles represent observed or directly measured variables while ovals represent unobserved or latent factors (derived from observed variables). Blue represents baseline characteristics before randomisation, green represents dose of CBD assumed during the RCT study, placebo (0 mg/kg/day) or active dose level (10, 20, or 25 mg/kg/day), red represents outcomes of interest, and purple represents latent variables.

Unidirectional arrows define a causal dependency, where one variable (cause) directly influences another (effect), and double-headed dashed arrows determine correlations between variables.