The socioeconomic burden of Dravet syndrome: a literature review

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INTRODUCTION AND OBJECTIVES

- Dravet syndrome (DS) is a severe infantile-onset epileptic encephalopathy, with an estimated incidence of 1 in 15,700 to 1 in 40,000 live births.[1-3]
- DS presents in the first year of life with characteristic seizures. Multiple seizure types that are frequently prolonged and refractory to antiepileptic drug treatment then develop. Developmental and cognitive slowing, behavioural disorders, mobility problems and other comorbidities appear during childhood.[4-6]
- Long-term outcome is generally poor, with ongoing seizures and a high mortality risk; patients present constant, demanding care needs to families and healthcare providers.[4-6]
- This structured literature review aimed to explore and understand the socioeconomic burden, impact and challenges presented by DS.

METHODS

Searches in literature databases

- The following literature databases were searched: MEDLINE (via Embase.com), Embase (via Embase.com), MEDLINE In-Process (via PubMed), EconLit (via EBSCO) and The Cochrane Library.
- Search strategy used MeSH and free-text DS terms, combined with: epidemiology, risk factors, natural history, comorbidities, symptoms, health-related quality of life, patient functioning and activities, caregivers, healthcare resource use, direct and indirect costs. Search restrictions included English language and human studies only; excluded were comments, letters, news articles and editorials. Additional searches were conducted in a variety of websites (**Table 1**).

Table 1: Searches in Websites and Conference Sites

Category	Website and Conference Sites
Conference proceedings[a]	American Epilepsy Society, International Epilepsy Congress, European Congress on Epileptology, International League Against Epilepsy
Key international HTA assessment websites	National Institute for Health and Care Excellence, Scottish Medicines Consortium, Haute Autorité de Santé, The Federal Joint Committee, Institute for Quality and Efficiency in Health Care, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Zorginstituut Nederland, International Network of Agencies for Health Technology Assessment
Sites for epidemiology, diagnosis and guidelines	World Health Organization
Clinical guidelines	TRIP database, Agency for Healthcare Research and Quality National Guideline Clearinghouse
Regulatory websites for approved treatments	US Food and Drug Administration, European Medicines Agency
Patient advocacy groups and registries	Dravet Syndrome Foundation, Dravet Syndrome European Federation, Intractable Childhood Epilepsy Alliance, SUDEP Action, Dravet syndrome International Patient Registry

Key: HTA, health technology assessment; TRIP, Turning Research into Practice; SUDEP, Sudden Unexpected Death in Epilepsy.
Notes: [a]Only abstracts published within 2 years or the last 2 conferences.

- Details of screening and data extraction processes are presented in **Figure 1**.

Figure 1: Screening of Articles and Data Extraction

- Titles and abstracts were screened for relevance against agreed inclusion/exclusion criteria
- For shortlisted articles, full-text articles were retrieved and screened against the same inclusion/exclusion criteria
- Inclusion criteria:
  - Article focused on Dravet syndrome (DS)
  - Presented information on at least one of the following: definitions and diagnosis of DS, clinical characteristics of patients, risk factors, disease progression, symptoms, incidence, prevalence and mortality (EU/US), humanistic burden on patients and carers, resource use and direct/indirect costs (EU/US), clinical guidelines (EU/US), treatment patterns (EU/US), or therapeutic options and HTA recommendations (EU/US)
- Data were extracted from all identified publications based on the above criteria

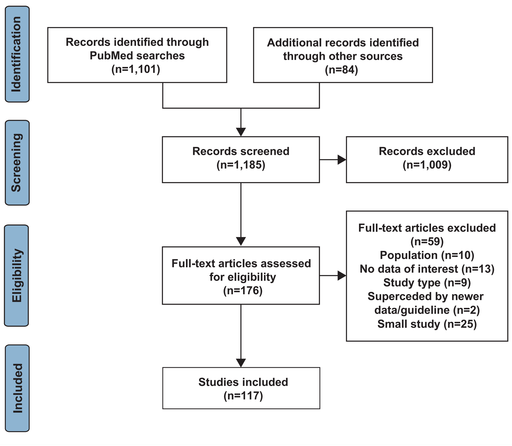
Key: HTA, health technology assessment.

RESULTS

Overview of the findings

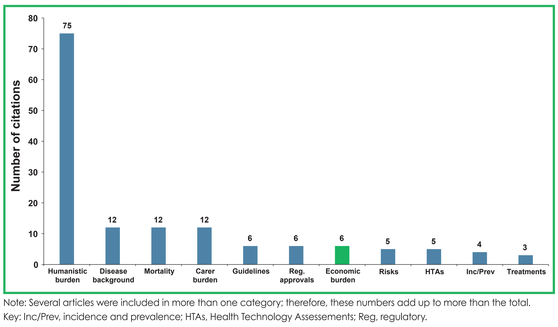
- Of 1,185 citations screened, 117 met the inclusion criteria (**Figure 2**; **Figure 3**).

Figure 2: PRISMA Flow Diagram



Note: Three relevant citations were found in 2 abstract books. These 3 publications are counted as individual citations.

Figure 3: Overview of Burden of Illness Literature Review - Categories of 117 Identified Citations



Note: Several articles were included in more than one category; therefore, these numbers add up to more than the total.
Key: Inc/Prev, incidence and prevalence; HTAs, Health Technology Assessements; Reg, regulatory.

Summary of literature describing economic burden in DS

- Evidence describing DS-associated resource use and/or economic burden was sparse; only 6 articles presenting relevant data were identified (**Table 2**).

Table 2: Resource Use and Economic Burden of Dravet Syndrome

Reference, Country	Study Design	Costs and Resource Use
Strzelczyk et al., 2014[7] Country: Germany	Retrospective study of healthcare use in DS patients (n=13) treated between 2007 and 2010	**Annual Direct Costs (2011 Costs) Mean (SD); % of Total Cost** Total direct costs: €6,506 (3,974) Medication (AEDs): €1,559 (1,356); 24% Other non-AED costs: €4,946 (4,136); 76% Hospitalisation: €4,483 (3,684); 68.9% Emergency transport service: €391 (903); 6.0% Outpatient care: €46 (56); 0.7% Diagnostic tests: €26 (42); 0.4%
Aras et al., 2015[8] Country: Pan-Europe	Online parent-reported survey for DS patients (n=274) (from May-June 2014)	**Patients (n [%]) With Admissions to the Emergency Room in the Last Year as a Result of Status Epilepticus** Number of Admissions / Total Population n=274 / Population With >4 Tonic Clonic Seizures n=124 0: 183 (67%); 83 (67%) 1: 42 (15%); 20 (16%) ≤2: 49 (18%); 21 (17%)
Skluzacek et al., 2011[9] Country: Canada	In 2004 and 2009, parents (n=81) of children with DS invited to participate in a survey regarding their child's condition and treatment	**Proportion of Parents (≥40%) Reporting Involvement of Specialists for Their Children and Young Adults With DS in 2009** Medical Specialists / Survey Respondents Reporting Involvement of This Specialty (%) General paediatrician – primary care provider: 100% Neurologist/epileptologist: 100% Speech pathologist: 89% Physical therapist: 80% Occupational therapist: 79% Geneticist: 63% Dietician: 54% Developmental or neuropsychiatrist/ psychologist: 49% Specialist in complementary medicine (osteopath): 46% Otolaryngologist (ENT)/audiologist: 43% Orthopaedist/orthotist: 41% Number of different medical specialities reported as providing care for children: 30. Other specialists seen by more than 10% of patients included: endocrinologist/metabolic specialist (38%), intensivist (critical care specialist) (38%), cardiologist (35%), emergency medicine specialist (32%), gastroenterologist (32%), developmental or neuro-ophthalmologist (28%), developmental/special needs dentist (27%), allergist (23%), immunologist (22%), sleep specialist (20%), urologist (14%), infectious disease specialist (12%), pulmonologist (11%).
Kuchenbuch et al., 2013[10] Country: France	Prospective cohort study in which DS patients (n=51) and their families answered a questionnaire on paediatric and adult care of DS patients	Education: 90% of patients in special education centres from 6 years old Treatments: Patients receiving polytherapy (98%), received a mean (SD) of 3.3 (0.93) AEDs Transfer to adult healthcare system: Transferred: 31 (61%), not transferred: 20 (39%) Visits to specialists: Of the 20 not transferring: 40% treated by child neurologist, 20% treated by adult neurologist, 20% treated by special institution physician (mostly psychiatrists), 15% had both adult and paediatric follow-up
SMC, 2008[11] Country: Scotland	HTA of stiripentol in combination with clobazam and valproate in DS patients	Cost (2008 costs) of stiripentol: £5,216 per year
AWMSG, 2008[12] Country: Wales	HTA of stiripentol in combination with clobazam and valproate in DS patients	Costs (2008 costs) Cost of stiripentol: £6,862 per patient per year (based on 30 kg child and a dose of 50 mg/kg/day) Cross boundary cost per seizure in Scotland: £4,555 Costs of day patient attendance at younger physically disabled services: £5,504

Key: AEDs, anti-epileptic drugs; AWMSG, All Wales Medicines Strategy Group; DS, Dravet syndrome; HTA, Health Technology Assessment; kg, kilogram; SD, standard deviation; SMC, Scottish Medicines Consortium.

- Only one article reported DS-associated direct costs (conducted in Germany; n=13 patients): total annual DS direct costs in 2011 were €6,506 per patient, hospitalisation being the main cost driver (68.9% total direct costs).[7]
- A pan-European study reported 33% of 274 DS patients requiring emergency room admissions for status epilepticus each year, 10% of these reported ≥4 admissions per year, some up to 30.[8]
- One survey of 81 parents of DS patients identified a total of 30 medical specialists providing care, including general paediatricians/primary care providers, neurologists/epileptologists (used in 100% of cases) and other specialists reported by ≥50% of parents: speech pathologists (89%), physical therapists (80%), occupational therapists (79%), geneticists (63%) and dieticians (54%).[9]
- DS patients require considerable carer support; parents accompanied their children on visits within paediatric (96%) and adult healthcare systems (94%), with a visit frequency of 4.8 and 6.1 months, respectively.[10]
- One study also reported 90% of DS patients to require specialised education from the age of 6 years old.[10]
- Although HTA submissions to the Scottish Medicines Consortium and the All Wales Medicines Strategy Group did not include formal economic evaluation, they reported stiripentol costs of £5,216 and £6,862 per patient per year, respectively.[11,12]

CONCLUSIONS

- This literature review reveals DS to significantly impact patients, their families and healthcare resources in managing not only the frequent and ongoing seizures but also the developmental, cognitive and behavioural issues and long-term comorbidities associated with the condition.
- The social and psychosocial impact of this devastating condition is well reported, although, as yet, unquantified.
- Our review also reveals economic evaluations (direct and indirect costs) in DS as minimal; however, the limited data available suggest resource use and economic burden presented by DS to be substantial.
- Further work is necessary to fully understand the economic burden presented by DS and the associated cost drivers.

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