Describing the Humanistic Burden of Illness in Dravet Syndrome – Important Questions Remain

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PURPOSE

- Dravet syndrome (DS), a severe infantile-onset genetic epileptic encephalopathy, presents in the first year of life with characteristic seizures[1,2]
- Multiple seizure types, developmental, cognitive, behavioural, and other debilitating problems develop during childhood
- Ongoing seizures and comorbidities impose demanding, long-term care needs on families and healthcare services[3-5]
- This review sought to understand this patient/caregiver burden and its humanistic impact

METHODS

Searches in Literature Databases and Websites

- Literature databases searched: MEDLINE, EMBASE, MEDLINE In-Process, EconLit, and The Cochrane Library, using MeSH and free-text DS terms, epidemiology, risk factors, natural history, comorbidities, symptoms, health-related quality of life (HRQoL), patient functioning/activities, caregivers, resource use, and costs
- Search restrictions: English language/human studies only; excluded comments, letters, news articles, and editorials. Additional website searches were conducted (**Table 1**). All were screened *vs* agreed inclusion/exclusion criteria

Table 1. Searches in Websites and Conference Sites

Category	Website and conference sites
Conference proceedings[a]	AES, IEC, ECE, ILAE
Key HTA websites	NICE, SMC, HAS, The Federal Joint Committee, IQEHC, Swedish HTA Agency, Zorginstituut Nederland, International HTA Agency Network
Epidemiology, diagnosis, clinical guidelines	WHO, TRIP database, Agency for Healthcare Research and Quality National Guideline Clearinghouse
Regulatory	US FDA, EMA
Patient advocacy groups	DS Foundation, DSEF, ICE, SUDEP Action, DS International Patient Registry

HTA, health technology assessment.

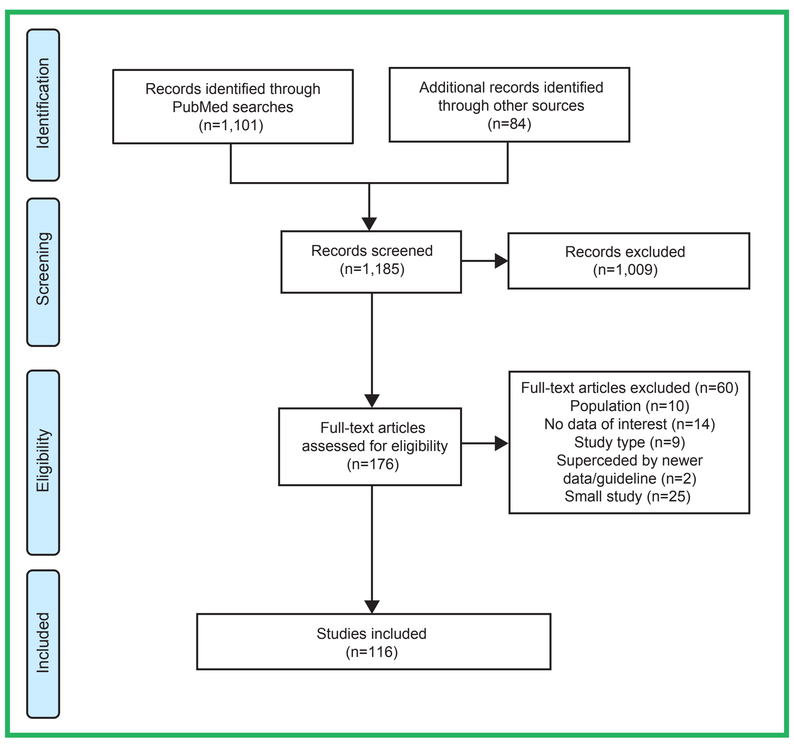
Only abstracts published within last 2 years/last 2 conferences.

RESULTS

Overview of Findings

- 1,184 citations were retrieved, 116 met study criteria (**Figure 1**), of which 75 described patient symptoms and humanistic burden, 12 described caregiver burden

Figure 1. PRISMA Flow Diagram



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

Summary of Literature Describing the Humanistic Burden in DS

Patient Burden

Symptoms and Features

- Seizure burden was most commonly reported, 70/116 (60.3%) articles
- Others commonly reported (≥50%): delayed language/communication (83%), growth slowing (70%), sleep disturbance (58%), ataxia (58%), body temperature dysregulation (57%), lack of social reserve/overly familiar to strangers (56%), hypotonia (56%), perseveration (52%), and nocturnal seizures (51%)[6]

HRQoL Burden

- **DS children showed worse HRQoL** *vs* healthy children ($p<0.001$) consistently decreasing with increasing age[7]
- **Independent predictors of a poorer HRQoL:** epilepsy severity, learning difficulties, age at first seizure, myoclonic seizures, and motor disorder ($p<0.05$)[7]

Caregiver Burden – Impact of DS

- Caregivers reported a number of negative impacts of caring for a DS child (**Table 2**)[6,8-16]

Table 2. Caregiver Burden in Dravet Syndrome

Reference, Objective, Study Design, Instruments Used[a]	Impact on Caregiver
Ragona *et al.*, 2015[8] To identify impact of caring for DS patients (n=13) on caregivers **Instruments:** MSPSS and structured interview[b]	**Family problems:** Difficulties finding respite care outside family; heavy impact of DS on caregivers' lives
Nolan *et al.*, 2006[9] To investigate how parents of DS patients (n=24) cope and care for their child **Instruments:** ICND questionnaire and semi-structured interview[b]	**Parents' views on managing children with stages 1–3 DS** **Stage 1: Prolonged, frightening convulsive seizures without developmental abnormalities** • 66.7% parents identified this 'significantly more difficult than other stages' ($p=0.03$) • Stress: uncertainty before diagnosis (81.2%); fear during prolonged seizures (25%); time in hospital (12.5%); waiting for seizure during febrile illness (12.5%) **Stage 2: Development of other seizure types plus developmental and behavioural problems** • 50% parents identified stage 2 'particularly difficult' • Stress: developmental delay (46.2%); behavioural problems (23.1%); loss of hopes for child's future (30.8%) **Stage 3: Better seizure control but declining cognitive abilities and increasing behavioural problems** • 8.3% parents described stage 3 'very difficult' • 78.6% parents reported negative impact on relationships
Welborn, *et al.*, 2010[10] To investigate clinical depression in family members of DS patients (n=22) **Instrument:** Online questionnaire	**Clinical depression in family** Sibling: 4.5%, Father: 9%, Mother: 9%, Maternal grandmother: 23%, Paternal grandfather: 4.5%
Genton, *et al.*, 2011[11] To report DS patient outcomes (n=24)	**Dependency of DS adult patients:** Live independently: 12.5%, Partly dependent: 33.3%, Totally dependent: 54.2%
Jansen, *et al.*, 2006[12] To analyse 14 SMEI adult phenotypes	**Dependency of patients in adulthood:** Live independently: 14.3%, Live in supervised community accommodation: 14.3%, Require considerable support for daily living: 71.4%, Attend special schools: 21.4%, Attend adult day care centres: 50%
Coqué, *et al.*, 2014[13] To assess AED administration by DS patient families (n=90)	**Caregivers preparing the drugs:** Mothers: 96%, Fathers: 58%, Grandparents: 51% **Caregivers administering drugs:** Mothers: 98%, Fathers: 61%, Grandparents: 57% **Issues:** Major error risk: 31%; Unhappy with texture/flavour of medicines: 75%; Parents ignorant of drug side effects: 13%
Desnous, *et al.*, 2011[14] To assess parents' (n=18) perception of fever in DS children	**Behaviour changes with fever:** 100% parents reported own behaviour changes with child's fever: 63% sleep in child's room; 42% wake child at night to monitor temperature/administer antipyretics; 89% children stay home with parental supervision when pyrexial **Impact of fever episodes on family life:** 89% parents stated fever impacts significantly on their social life (less interaction with fever episodes), 84% their professional life; 88.2% reported managing fever differently in DS child siblings
Granata *et al.*, 2011[15] To report parents' perception of DS	• Anxiety regarding DS diagnosis (e.g. "*I don't trust your diagnosis because my child is normal*") • Parental stress (e.g. "*I am afraid he will die during a seizure*") • Dilemmas between disclosing/denying mental difficulties; loss of hope for child's future; difficulties in dealing with sick child • Familial and social relationships (e.g. "*We have never been out to dinner since the disease*") • Parental insights on siblings (e.g. "*The brother shows some issues; I think he is angry or jealous*") • Difficulty in finding respite care (e.g. "*This is not so easy, and trying to live a serene life requires psychological and material support that is often difficult to find*")
Skluzacek, *et al.*, 2011[6] To understand DS parental concerns (2004 survey, n=65; 2009 survey n=86)	• 86% respondents acknowledged experiencing grief regarding child's condition • 89% participating parents affirmed need for support to manage ongoing stress of child care • Parents admitted to requiring additional advocacy/support to optimise development and HRQoL, to access specialised medical care, to optimise development and HRQoL; financial support; emotional support; opportunities to participate in research
Nolan, *et al.*, 2008[16] To identify practical suggestions to improve life of families with DS child (interview n=24)	• 88% children had behavioural problem history, 76% families believed siblings resentful of increased attention paid to the DS child, 71% families had childcare difficulties • Families reported negative impacts on spousal relationships due to stress of caring for DS child

DS, Dravet syndrome; ICND, Impact of Childhood Neurological Disability scale; MSPSS, Multidimensional Scale of Perceived Social Support.

[a]Instruments are only listed where used; [b]Semi-structured and structured interviews grouped as one instrument.

Instruments Used to Assess Humanistic Burden in DS

- 33 different instruments measured patient and caregiver burden (**Table 3**)

Table 3. Instruments Used to Measure Patient/Caregiver Burden in Dravet Syndrome

Symptoms Evaluated	No. Instruments	No. References Using Instruments
Behavioural	9	5
Cognitive impairment	10	13
Motor	6	8
Sleep disturbance	1	1
Multiple symptoms	2	6
HRQoL	4	1
Caregiver burden	4	3

CONCLUSIONS

- The substantial seizure burden associated with DS is well characterised
- Additional developmental, cognitive/behavioural issues and long-term comorbidities associated with DS present a substantial burden on both patients and caregivers
- This caregiver burden is likely underestimated given the lack of a validated DS-specific instrument for its measurement
- This review identified the need for:
  - Validated instruments to quantify the HRQoL burden in both DS patients and their caregivers
  - More substantive work to better describe and quantify the humanistic and socioeconomic burden of DS on patients and their caregivers

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