

Temporal Changes in reporting of neurodevelopmental outcomes after maternal exposure to valproate – a contribution of the ConcePTION project, Journal: Drug Safety

Authors: Dimitra Gkolfi, Yrea R. J. van Rijt-Weetink, Henric Taavola, Lovisa Sandberg, Boukje C. Raemaekers, Florence P. A. M. van Hunsel, Anneke L.M. Passier, Eugène P. van Puijenbroek.

Corresponding author: E.P. van Puijenbroek, e.p.van.puijenbroek@rug.nl, Groningen Research Institute of Pharmacy, Pharmacotherapy, -Epidemiology and -Economics, University of Groningen, Groningen, The Netherlands and Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands

Supplementary material Table T1

Selected MedDRA® preferred terms related to neurodevelopmental outcomes.

Preferred term number	Preferred term	Grouped preferred terms
10012557	Developmental coordination disorder	Motor function disorders
10066088	Fine motor delay	
10076288	Fine motor skill dysfunction	
10069118	Gross motor delay	
10070302	Motor developmental delay	
10008129	Cerebral palsy	
10037213	Psychomotor retardation	
10049215	Psychomotor skills impaired	
10012559	Developmental delay	Developmental Delay
10076709	Developmental regression	
10064062	Neurodevelopmental disorder	
10056405	Mentally late developer	Intellectual disabilities
10067989	Intellectual disability	
10057668	Cognitive disorder	
10027374	Mental impairment	
10041467	Speech disorder developmental	Communication disorders
10041466	Speech disorder	
10078970	Cognitive linguistic deficit	
10074869	Language disorder	
10037999	Reading disorder	Learning disorders
10024092	Learning disability	
10061265	Learning disorder	
10083622	Attention deficit hyperactivity disorder	Attention deficit hyperactivity
10003746	Atypical attention deficit syndrome	
10013496	Disturbance in attention	
10063844	Autism spectrum disorder	Disorders of autism spectrum
10077516	Sensory processing disorder	

Selection based on MedDRA® 26.0- English

Supplementary material Table T2

MedDRA® preferred terms not taken into account for cluster analysis

- 10064998 Drug exposure before pregnancy
- 10073513 Exposure during pregnancy
- 10071409 Foetal exposure during delivery
- 10071404 Foetal exposure during pregnancy
- 10071405 Foetal exposure timing unspecified
- 10026923 Maternal drugs affecting foetus
- 10071406 Maternal exposure before pregnancy
- 10071407 Maternal exposure during delivery
- 10071408 Maternal exposure during pregnancy
- 10071415 Maternal exposure timing unspecified

Selection based on MedDRA® 26.0- English

Supplementary material; Figures S1, S2, S3, S4

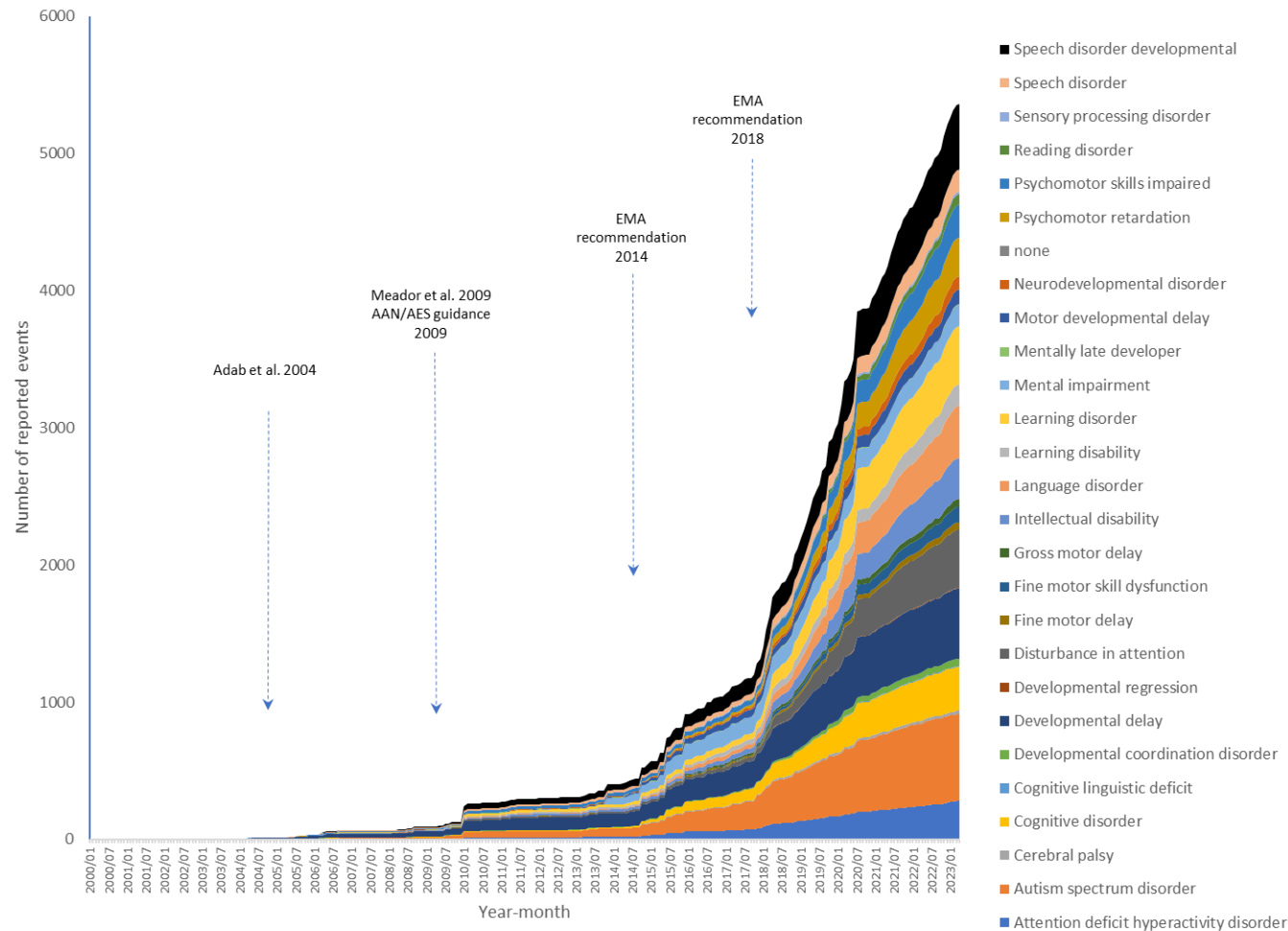


Figure S1. Cumulative number of reported preferred terms of neurodevelopmental outcomes and valproate exposure during pregnancy; the dotted lines represent the moments in time of key publications and regulatory decisions taken. A report may concern multiple preferred terms. Only the number of reported events after Jan 1st, 2000 are shown.

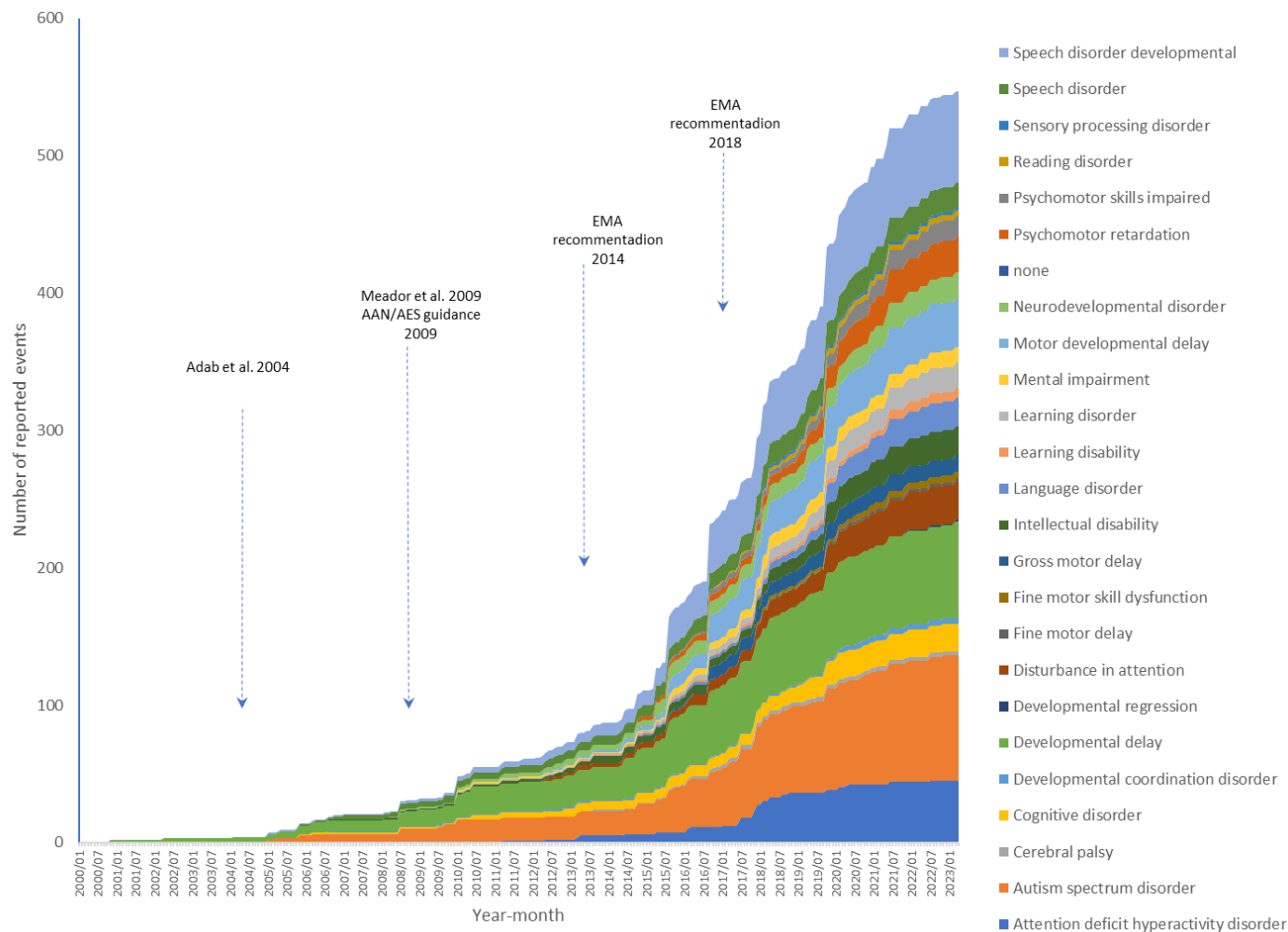


Figure S2. Cumulative number of reported preferred terms of neurodevelopmental outcomes and carbamazepine/lamotrigine exposure during pregnancy; the dotted lines represent the moments in time of key publications and regulatory decisions taken. A report may concern multiple preferred terms. Only the number of reported events after Jan 1st, 2000 are shown.

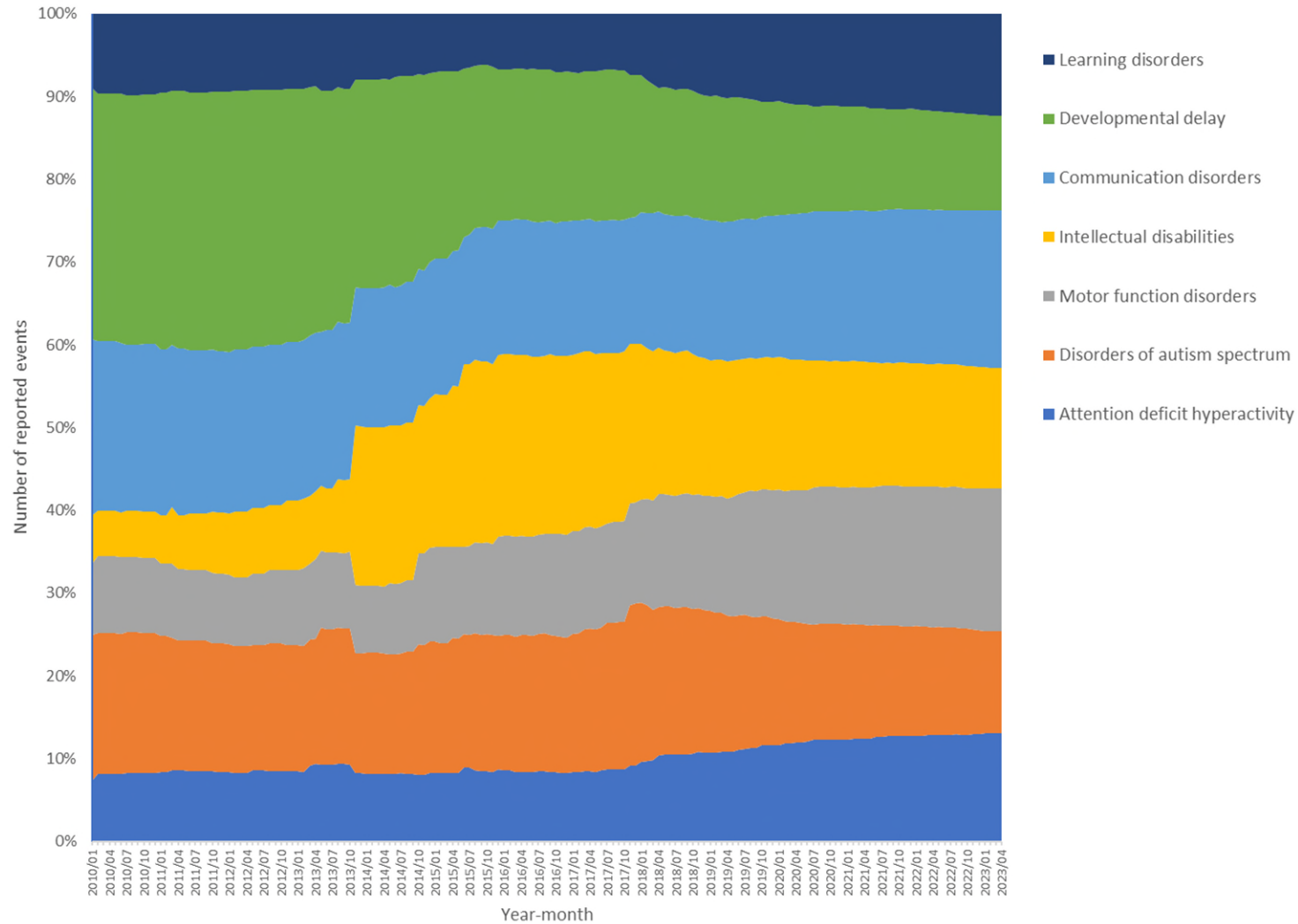


Figure S3. Relative contributions of the main groups of preferred terms related to neurodevelopmental outcomes and valproate exposure during pregnancy; the dotted lines represent the moments in time of key publications and regulatory decisions taken. A report may concern multiple preferred terms. Only the number of reported events after Jan 1st, 2010 are shown.

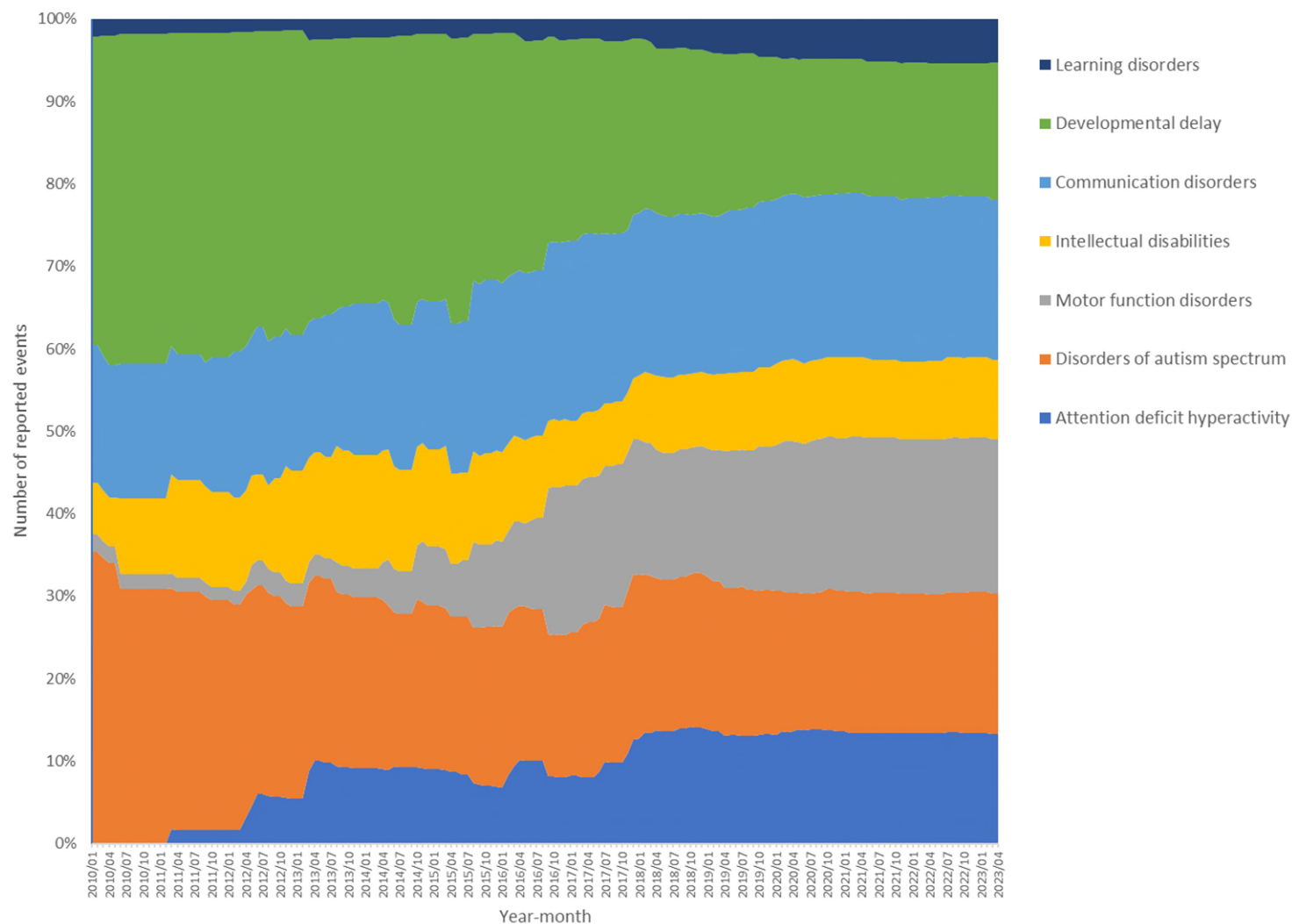


Figure S4. Relative contributions of the main groups of preferred terms related to neurodevelopmental outcomes and exposure to the comparator drugs (carbamazepine and lamotrigine) during pregnancy; the dotted lines represent the moments in time of key publications and regulatory decisions taken. A report may concern multiple preferred terms. Only the number of reported events after Jan 1st, 2010 are shown.

Supplementary material Table T3

Clusters identified as showing signs of NDO

Cluster 2009-1 (90 reports)	
Foetal anticonvulsant syndrome	74 / 90
Developmental delay	23 / 90
Dysmorphism	8 / 90

Cluster 2009-2 (9 reports)	
Dysmorphism	6 / 9
Congenital nose malformation	5 / 9
Multiple congenital abnormalities	4 / 9
Congenital musculoskeletal disorder	4 / 9
Foetal anticonvulsant syndrome	4 / 9
Low set ears	3 / 9
Cardiac murmur	3 / 9
Congenital anomaly	3 / 9
Joint contracture	3 / 9
Developmental delay	3 / 9
Respiratory disorder	2 / 9
Cryptorchism	2 / 9
Feeding disorder	2 / 9
Hypertonia	2 / 9
Lip disorder	2 / 9
Apnoea	2 / 9
Pallor	2 / 9
Cyanosis	2 / 9
Hypokinesia	2 / 9
Gastroesophageal reflux disease	2 / 9
Speech disorder developmental	2 / 9
Ear infection	2 / 9
Unevaluable event	2 / 9
Atrial septal defect	2 / 9
Cognitive disorder	2 / 9
Tracheomalacia	2 / 9
Language disorder	2 / 9
Congenital musculoskeletal disorder of limbs	2 / 9
Premature baby	1 / 9
Agitation neonatal	1 / 9
Blood thyroid stimulating hormone increased	1 / 9
Tremor	1 / 9

Cardiac failure congestive	1 / 9
Irritability	1 / 9
Cerebral atrophy congenital	1 / 9
Petechiae	1 / 9
Hyperreflexia	1 / 9
Gingival hypertrophy	1 / 9
Hypertelorism	1 / 9
Haematoma	1 / 9
Respiratory distress	1 / 9
Hypoventilation neonatal	1 / 9
Pulmonary oedema	1 / 9
Hypoventilation	1 / 9
Poor sucking reflex	1 / 9
Micrognathia	1 / 9
Penis disorder	1 / 9
Hydrocele	1 / 9
Congenital foot malformation	1 / 9
Skin discolouration	1 / 9
Neonatal disorder	1 / 9
Heart disease congenital	1 / 9
Foetal heart rate increased	1 / 9
Poor feeding infant	1 / 9
Metabolic acidosis	1 / 9
Small for dates baby	1 / 9
Anaemia	1 / 9
Heart rate decreased	1 / 9
Umbilical cord around neck	1 / 9
Sluggishness	1 / 9
Thrombocytopenia	1 / 9
Carnitine decreased	1 / 9
Respiratory rate increased	1 / 9
Foot deformity	1 / 9
Brachycephaly	1 / 9
Congenital jaw malformation	1 / 9
Fatigue	1 / 9
Congenital oral malformation	1 / 9
Gastroenteritis	1 / 9
Joint range of motion decreased	1 / 9
Joint instability	1 / 9
Stridor	1 / 9
Anal erythema	1 / 9
Aspiration	1 / 9
Selective eating disorder	1 / 9
Tachycardia	1 / 9
Dilatation ventricular	1 / 9
Pain	1 / 9

Upper respiratory tract infection	1 / 9
Cough	1 / 9
Movement disorder	1 / 9
Extremity contracture	1 / 9
Dacryostenosis acquired	1 / 9
Retching	1 / 9
Hernia congenital	1 / 9
Rash	1 / 9
Growth retardation	1 / 9
Congenital hearing disorder	1 / 9
Hypoglycaemia	1 / 9
Acoustic stimulation tests abnormal	1 / 9
Asthenia	1 / 9
Diarrhoea	1 / 9
Testicular swelling	1 / 9
Trismus	1 / 9
Weight decreased	1 / 9
Cerebral dysgenesis	1 / 9
Dysphagia	1 / 9
Abdominal pain	1 / 9
Gait disturbance	1 / 9
Microcephaly	1 / 9
Focal dyscognitive seizures	1 / 9
Congenital eye disorder	1 / 9
Bronchitis	1 / 9
Incontinence	1 / 9
Screaming	1 / 9
Antisocial behaviour	1 / 9
Wheezing	1 / 9
Hyperacusis	1 / 9
Ear malformation	1 / 9
Disturbance in attention	1 / 9
Nasal congestion	1 / 9
Abnormal behaviour	1 / 9
Communication disorder	1 / 9
Eye disorder	1 / 9
Psychopathic personality	1 / 9
Coordination abnormal	1 / 9
Dysarthria	1 / 9
General physical health deterioration	1 / 9
Aggression	1 / 9
Sleep disorder	1 / 9
Speech disorder	1 / 9
Joint dislocation	1 / 9
Syndactyly	1 / 9
Congenital hydrocephalus	1 / 9

Muscle tightness	1 / 9
Blindness	1 / 9
Cleft palate	1 / 9
Seizure	1 / 9
Ten disorder	1 / 9
Ventricular hypertrophy	1 / 9
Laryngomalacia	1 / 9
Aorta hypoplasia	1 / 9

Cluster 2014-1 (209 reports)

Pain	207 / 209
Emotional distress	207 / 209
Deformity	206 / 209
Physical disability	201 / 209
Anhedonia	158 / 209
Multiple injuries	113 / 209
Spina bifida	106 / 209
Tension	98 / 209
Injury	93 / 209
Impaired work ability	82 / 209
Loss of employment	72 / 209
Anxiety	71 / 209
Neural tube defect	60 / 209
Social problem	54 / 209
Quality of life decreased	54 / 209
Multiple congenital abnormalities	46 / 209
Congenital cardiovascular anomaly	42 / 209
Heart disease congenital	41 / 209
Loss of personal independence in daily activities	39 / 209
Economic problem	23 / 209
Dissociation	21 / 209
Congenital anomaly	20 / 209

Cluster 2014 -2 (185 reports)

Foetal anticonvulsant syndrome	144 / 185
Dysmorphism	91 / 185
Developmental delay	77 / 185
Speech disorder developmental	43 / 185
Autism spectrum disorder	37 / 185
Abnormal behaviour	28 / 185
Learning disorder	21 / 185
Psychomotor skills impaired	20 / 185
Hypospadias	15 / 185

Cluster 2018-1 (639 reports)	
Foetal anticonvulsant syndrome	315 / 639
Autism spectrum disorder	162 / 639
Developmental delay	112 / 639
Dysmorphism	103 / 639
Speech disorder developmental	76 / 639
Learning disorder	42 / 639

Cluster 2018 -2 (75 reports)	
Foetal anticonvulsant syndrome	50 / 75
Dysmorphism	36 / 75
Autism spectrum disorder	32 / 75
Speech disorder developmental	30 / 75
Developmental delay	28 / 75
Learning disorder	24 / 75
Attention deficit hyperactivity disorder	21 / 75
Disturbance in attention	17 / 75
Asthma	16 / 75
Hypermobility syndrome	15 / 75
Speech disorder	14 / 75
Dyspraxia	14 / 75
Hypotonia	13 / 75
Hyperacusis	12 / 75
Abnormal behaviour	12 / 75
Foot deformity	12 / 75
Visual impairment	12 / 75
Unevaluable event	11 / 75
Aggression	11 / 75
Behaviour disorder	11 / 75
Sleep disorder	10 / 75
Learning disability	10 / 75
Anxiety	10 / 75
Memory impairment	10 / 75
Astigmatism	9 / 75
Ear infection	9 / 75
Language disorder	9 / 75
Coordination abnormal	9 / 75
Talipes	9 / 75
Pain in extremity	9 / 75
Gastroesophageal reflux disease	9 / 75
Fatigue	9 / 75
Cognitive disorder	8 / 75
Communication disorder	8 / 75
Hypoacusis	8 / 75

Strabismus	8 / 75
Dyslexia	8 / 75
Disability	8 / 75
Deafness	8 / 75
Incontinence	7 / 75

Cluster 2018 -3 (56 reports)

Dysmorphism	42 / 56
Foetal anticonvulsant syndrome	31 / 56
Developmental delay	22 / 56
Foot deformity	21 / 56
Intellectual disability	21 / 56
Autism spectrum disorder	20 / 56
Speech disorder developmental	20 / 56
Behaviour disorder	16 / 56
Anxiety	16 / 56
Enuresis	16 / 56
Cognitive disorder	15 / 56
Strabismus	15 / 56
Ear infection	14 / 56
Hypotonia	14 / 56
Learning disorder	14 / 56
Psychomotor retardation	13 / 56
Visual impairment	13 / 56
Nasal disorder	13 / 56
Knee deformity	12 / 56
Psychomotor skills impaired	12 / 56
Speech disorder	12 / 56
Scoliosis	12 / 56
Oropharyngeal discomfort	12 / 56
Ear disorder	12 / 56
Disturbance in attention	12 / 56
Low set ears	12 / 56
Sleep disorder	10 / 56
Astigmatism	10 / 56
Lip disorder	10 / 56
Hypertelorism	10 / 56
Epilepsy	10 / 56
Pectus excavatum	10 / 56
Language disorder	10 / 56
Dysgraphia	9 / 56
Congenital foot malformation	9 / 56
Disorientation	9 / 56
Dyspraxia	9 / 56
Congenital hand malformation	9 / 56

Bronchitis	8 / 56
Fine motor skill dysfunction	8 / 56
Congenital musculoskeletal disorder of skull	8 / 56
Cryptorchism	8 / 56
Multiple congenital abnormalities	8 / 56
Aggression	8 / 56
Atrial septal defect	8 / 56
Motor developmental delay	8 / 56
Echolalia	7 / 56
Joint laxity	7 / 56
Prominent epicanthal folds	7 / 56
Congenital nose malformation	7 / 56
Respiratory distress	7 / 56
Nasopharyngitis	7 / 56
Congenital anomaly	7 / 56
Personality disorder	6 / 56
Encopresis	6 / 56
Attention deficit hyperactivity disorder	6 / 56
Educational problem	6 / 56
Psychomotor hyperactivity	6 / 56
Inguinal hernia	6 / 56
Motor dysfunction	6 / 56
Syndactyly	6 / 56
Cleft palate	6 / 56
Cough	6 / 56
Clinodactyly	6 / 56
Nipple disorder	6 / 56
Balance disorder	6 / 56
Memory impairment	5 / 56

Cluster 2018 -4 (88 reports)

Pain	68 / 88
Anhedonia	67 / 88
Emotional distress	65 / 88
Cognitive disorder	59 / 88
Abnormal behaviour	54 / 88
Injury	54 / 88
Economic problem	51 / 88
Autism spectrum disorder	51 / 88
Developmental delay	38 / 88
Nervous system disorder	35 / 88
Mental impairment	34 / 88
Attention deficit hyperactivity disorder	31 / 88
Speech disorder developmental	24 / 88
Motor developmental delay	23 / 88
Mental disorder	22 / 88

Dysmorphism	21 / 88
Congenital anomaly	21 / 88
Loss of personal independence in daily activities	20 / 88
Physical disability	19 / 88
Language disorder	17 / 88
Social problem	15 / 88
Illiteracy	14 / 88
Foetal anticonvulsant syndrome	14 / 88
Congenital nose malformation	14 / 88
Sensory disturbance	12 / 88
Speech disorder	11 / 88
Multiple injuries	11 / 88
Communication disorder	10 / 88
Hypotonia	9 / 88
Loss of employment	9 / 88
Impaired self-care	9 / 88
Anxiety	8 / 88

Cluster 2023-1 (1179 reports)

Foetal anticonvulsant syndrome	453 / 1179
Autism spectrum disorder	302 / 1179
Developmental delay	183 / 1179
Dysmorphism	165 / 1179
Speech disorder developmental	112 / 1179

Cluster 2023 -2 (91 reports)

Pain	68 / 91
Anhedonia	67 / 91
Emotional distress	66 / 91
Cognitive disorder	62 / 91
Abnormal behaviour	59 / 91
Injury	54 / 91
Economic problem	51 / 91
Autism spectrum disorder	51 / 91
Developmental delay	44 / 91
Mental impairment	36 / 91
Attention deficit hyperactivity disorder	35 / 91
Nervous system disorder	35 / 91
Speech disorder developmental	25 / 91
Motor developmental delay	24 / 91
Mental disorder	23 / 91
Dysmorphism	22 / 91
Congenital anomaly	22 / 91
Loss of personal independence in daily activities	20 / 91
Physical disability	20 / 91

Language disorder	19 / 91
Speech disorder	15 / 91
Illiteracy	14 / 91
Foetal anticonvulsant syndrome	14 / 91
Social problem	13 / 91
Sensory disturbance	12 / 91
Anxiety	11 / 91
Multiple injuries	11 / 91
Communication disorder	10 / 91
Congenital nose malformation	9 / 91

Cluster 2023 -3 (590 reports)	
Dysmorphism	437 / 590
Disturbance in attention	339 / 590
Behaviour disorder	316 / 590
Speech disorder developmental	308 / 590
Learning disorder	307 / 590
Language disorder	283 / 590
Psychomotor retardation	233 / 590
Autism spectrum disorder	223 / 590
Anxiety	218 / 590
Ear disorder	214 / 590
Developmental delay	214 / 590
Intellectual disability	207 / 590
Dysgraphia	204 / 590
Cognitive disorder	203 / 590
Nasal disorder	201 / 590
Hypotonia	189 / 590
Psychomotor skills impaired	186 / 590
Visual impairment	183 / 590
Oropharyngeal discomfort	181 / 590
Foot deformity	177 / 590
Enuresis	173 / 590
Ear infection	170 / 590
Fatigue	168 / 590
Memory impairment	164 / 590
Attention deficit hyperactivity disorder	154 / 590
Foetal anticonvulsant syndrome	153 / 590
Scoliosis	150 / 590
Sleep disorder	138 / 590
Nasopharyngitis	130 / 590
Strabismus	128 / 590
Educational problem	117 / 590
Talipes	115 / 590
Dyspraxia	113 / 590
Aggression	112 / 590

Astigmatism	110 / 590
Communication disorder	104 / 590
Balance disorder	104 / 590
Fine motor skill dysfunction	102 / 590
Bronchitis	100 / 590
Gastroesophageal reflux disease	100 / 590
Myopia	98 / 590
Disorientation	95 / 590
Speech disorder	94 / 590
Congenital musculoskeletal disorder of limbs	92 / 590
Joint laxity	89 / 590
Personal relationship issue	84 / 590
Learning disability	81 / 590
Bronchiolitis	80 / 590
Rhinitis	78 / 590
Gait disturbance	77 / 590
Coordination abnormal	76 / 590
Hypermobility syndrome	75 / 590
Knee deformity	75 / 590
Eating disorder	74 / 590
Dyslexia	71 / 590
Inguinal hernia	69 / 590
Hypertonia	67 / 590
Cough	67 / 590
Executive dysfunction	66 / 590
Neurodevelopmental disorder	64 / 590
Reading disorder	63 / 590
Cryptorchism	62 / 590
Social avoidant behaviour	62 / 590
Frustration tolerance decreased	61 / 590
Asthma	61 / 590
Mental disorder	60 / 590
Epilepsy	59 / 590
Hypertelorism	59 / 590
Plagiocephaly	57 / 590

Cluster 2023 -4 (74 reports)	
Dysmorphism	48 / 74
Foetal anticonvulsant syndrome	43 / 74
Congenital nose malformation	31 / 74
Atrial septal defect	22 / 74
Congenital musculoskeletal disorder of limbs	21 / 74
Hypertelorism	19 / 74
Congenital musculoskeletal disorder of skull	17 / 74
Developmental delay	16 / 74
Lip disorder	14 / 74

Prominent epicanthal folds	12 / 74
Low set ears	12 / 74
Autism spectrum disorder	11 / 74
Congenital hand malformation	11 / 74
Craniosynostosis	11 / 74
Nipple disorder	10 / 74
Hypotonia	10 / 74
Ventricular septal defect	10 / 74
Craniofacial deformity	10 / 74
Cardiac murmur	9 / 74
Hypospadias	9 / 74
Micrognathia	9 / 74
Congenital oral malformation	9 / 74
Speech disorder developmental	9 / 74
Clinodactyly	8 / 74
Ear malformation	8 / 74
Congenital anomaly	8 / 74
Anomaly of external ear congenital	8 / 74
Foot deformity	7 / 74

Cluster 2023 -5 (22 reports)	
Foetal anticonvulsant syndrome	16 / 22
Autism spectrum disorder	13 / 22
Asthma	11 / 22
Dysmorphism	11 / 22
Learning disability	10 / 22
Speech disorder developmental	10 / 22
Developmental delay	9 / 22
Dyspraxia	9 / 22
Illness	8 / 22
Deafness	8 / 22
Hyperacusis	8 / 22
Incontinence	7 / 22
Talipes	7 / 22
Hypermobility syndrome	7 / 22
Cerebral palsy	7 / 22
Epilepsy	6 / 22
Unevaluable event	6 / 22
Mental disability	5 / 22
Disability	4 / 22
Hypotonia	3 / 22
Cardiac failure	3 / 22
Physical disability	3 / 22
Spina bifida	2 / 22

Cluster 2023 -6 (6 reports)

Epilepsy congenital	3 / 6
Developmental hip dysplasia	2 / 6
Ataxia	1 / 6
Strabismus congenital	1 / 6
Psychomotor skills impaired	1 / 6
Dysmorphism	1 / 6
Speech disorder developmental	1 / 6
Hypotonia	1 / 6
Dysphagia	1 / 6
Congenital joint malformation	1 / 6
Abdominal pain	1 / 6
Excessive ocular convergence	1 / 6
Pelvic deformity	1 / 6
Back pain	1 / 6
Otitis media	1 / 6
Congenital anomaly	1 / 6
Congenital monorchidism	1 / 6
Monorchidism	1 / 6

Supplementary material Table T4

Number of reported preferred terms that belong to groups of terms related to Neurodevelopmental outcomes for both carbamazepine and lamotrigine.

Group of preferred terms related to Neurodevelopmental disorders	Carbamazepine (%)	Lamotrigine (%)
Developmental delay	42 (19.7%)	49 (14.7%)
Attention & hyperactivity disorders	25 (11.7%)	48(14.4%)
Autism spectrum disorders	46 (21.6%)	47 (14.1%)
Motor function disorders	28 (13.1%)	74 (22.2%)
Intellectual disabilities	24 (11.3%)	29 (8.7%)
Communication disorders	36 (16.9%)	70 (21.0%)
Learning disorders	12 (5.6%)	17 (5.1%)
Total	213	334