Journal: Clinical Drug Investigation

THERAPEUTIC STRATEGIES AFTER DISCONTINUATION OF VALPROATE BY FEMALES WITH EPILEPSY OF CHILD-BEARING POTENTIAL: AN INSURANCE CLAIMS DATABASE STUDY IN FRANCE AND THE UNITED KINGDOM

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ONLINE RESOURCE (SUPPLEMENTARY MATERIAL)

Online Resource Table S1. Antiseizure medication treatments after valproate discontinuation: SNDS

LOW VPA REINTRODUCTION PATTERNS	N = 4,941 (67.3%)
Cluster 1: Principally no ASM treatment at all	N = 2,036 (27.7%)
At least one ASM delivered	
Monotherapy (without VPA)	395 (19.4%)
Dual therapy (without VPA)	97 (4.8%)
Combination therapy (without VPA)	20 (1.0%)
VPA alone	601 (29.5%)
VPA + 1 other ASM	295 (14.5%)
VPA + 2 other ASMs	91 (4.5%)
VPA + ≥3 other ASMs	48 (2.4%)
≥ 1 month without any ASM, n (%)	**2,036 (100%)**
Cluster 2 Principally 1 ASM (without VPA)	N = 1,871 (25.5%)
At least one ASM delivered	
Monotherapy (without VPA)	1,871 (100%)
Lamotrigine	927 (49.5%)
Levetiracetam	692 (37.0%)
Topiramate	102 (5.5%)
Other ASM	71 (3.8%)
Dual therapy (without VPA)	444 (23.7%)
Combination therapy (without VPA)	46 (2.5%)
VPA alone	52 (2.8%)
VPA + 1 other ASM	195 (104%)
VPA + 2 other ASMs	34 (1.8%)
VPA + ≥3 other ASMs	14 (0.7%)
≥ 1 month without any ASM, n (%)	**704 (37.6%)**
Cluster 3 Principally 2 ASMs (without VPA)	N = 737 (10.0%)
At least one ASM delivered	
Monotherapy (without VPA)	334 (45.3%)
Dual therapy (without VPA)	737 (100%)
Lamotrigine + levetiracetam	172 (23.3%)
Lamotrigine + clobazepam	122(16.0%)
Levatiracetam + clobazepam	74(10.0%)
Lamotrigine + topiramate	38(6.2%)
Other pairings of ASMs	325 (44.1%)
Combination therapy (without VPA)	222 (30.1%)
VPA alone	14 (1.9%)
VPA + 1 other ASM	30 (4.1%)
VPA + 2 other ASMs	83 (11.3%)
VPA + ≥3 other ASMs	20 (2.7%)
≥ 1 month without any ASM, n (%)	**148 (20.1%)**
Cluster 4 Principally ≥3 ASMs (without VPA)	N = 297 (4.0%)

HIGH VPA REINTRODUCTION PATTERNS	N = 2,404 (32.7%)
Cluster 5: Principally VPA monotherapy	N = 1,286 (17.5%)
At least one ASM delivered	
Monotherapy (without VPA)	123 (9.6%)
Dual therapy (without VPA)	27 (2.1%)
Combination therapy (without VPA)	≤10
VPA monotherapy	1,286 (100%)
VPA + 1 other ASM	168 (13.1%)
VPA + 2 other ASMs	12 (0.9%)
VPA + ≥3 other ASMs	0
≥ 1 month without any ASM, n (%)	**1,271 (98.8%)**
Cluster 6: Principally VPA + one other ASM	N = 760 (10.3%)
At least one ASM delivered	
Monotherapy (without VPA)	433 (57.0%)
Dual therapy (without VPA)	76 (10.0%)
Combination therapy (without VPA)	21 (28%)
VPA alone	126 (16.6%)
VPA + 1 other ASM	756 (99.5%)
VPA + lamotrigine	262 (34.5%)
VPA + levetiracetam	144 (18.9%)
VPA + clobazepam	96 (126%)
VPA + topiramate	70 (9.2%)
VPA + carbamazepine	42 (5.5%)
VPA + 1 other ASM	124 (16.4%)
VPA + 2 other ASMs	131(17.2%)
VPA + ≥3 other ASMs	20 (2.6%)
≥ 1 month without any ASM, n (%)	**548 (72.1%)**
Cluster 7 Principally VPA + 2 other ASMs	N = 358 (4.9%)
At least one ASM delivered	
Monotherapy (without VPA)	126 (35.2%)
Dual therapy (without VPA)	160 (44.7%)
Combination therapy (without VPA)	41 (11.5%)
VPA alone	≤10
VPA + 1 other ASM	89 (24.9%)
VPA + 2 other ASMs	337 (94.1%)
VPA + lamotrigine + clobazepam	51 (14.2%)
VPA + lamotrigine + levetiracetam	29 (8.1%)
VPA + levatiracetam + clobazepam	20 (5.6%)
VPA + Other pairings of ASMs	245 (72.7%)
VPA + ≥3 other ASMs	92 (25.7%)
≥ 1 month without any ASM, n (%)	**227 (63.4%)**

At least one ASM delivered	
Monotherapy (without VPA)	54 (18.2%)
Dual therapy (without VPA)	165 (55.6%)
Combination therapy (without VPA)	297 (100%)
Lamotrigine + levetiracetam + clobazepam	43 (14.5%)
Other combinations	
VPA alone	274 (92.3%)
VPA + 1 other ASM	0
VPA + 2 other ASMs	≤10
VPA + ≥3 other ASMs	19 (6.4%)
≥ 1 month without any ASM, n (%)	45 (15.2%)
	41 (13.8%)

ASM: antiseizure medication; SNDS: *Système National des Données de Santé;* VPA: valproate.
The treatment indicated in blue is the modal treatment for the Pattern.

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Online Resource Table S2. Antiseizure medication treatments after valproate discontinuation: CPRD

LOW VPA REINTRODUCTION PATTERNS	N = 177 (49.4%)	**HIGH VPA REINTRODUCTION PATTERNS**	N = 181 (50.6%)
Cluster 1: Principally no ASM treatment at all	N = 75 (20.9%)	Cluster 5: Principally VPA monotherapy	N = 86 (24.0%)
At least one ASM delivered		**At least one ASM delivered**	
Monotherapy (without VPA)	6 (8.0%)	Monotherapy (without VPA)	5 (5.8%)
Dual therapy (without VPA)	0	Dual therapy (without VPA)	0
Combination therapy (without VPA)	0	Combination therapy (without VPA)	0
VPA alone	12 (16.0%)	VPA monotherapy	86 (100%)
VPA + 1 other ASM	3 (4.0%)	VPA + 1 other ASM	5 (5.8%)
VPA + 2 other ASMs	0	VPA + 2 other ASMs	0
VPA + ≥3 other ASMs	0	VPA + ≥3 other ASMs	0
≥ 1 month without any ASM, n (%)	**75 (100%)**	**≥ 1 month without any ASM, n (%)**	**86 (100%)**
Cluster 2 Principally 1 ASM (without VPA)	N = 74 (20.7%)	Cluster 6: Principally VPA + one other ASM	N = 41 (11.5%)
At least one ASM delivered		**At least one ASM delivered**	
Monotherapy (without VPA)	74 (100%)	Monotherapy (without VPA)	26 (63.4%)
Lamotrigine	23 (31.1%)	Dual therapy (without VPA)	2 (4.9%)
Levetiracetam	40 54.1%)	Combination therapy (without VPA)	1 (2.4%)
Other ASM	16 (21.6%)	VPA alone	10 (24.4%)
Dual therapy (without VPA)	12 (23.7%)	VPA + 1 other ASM	41 (100%)
Combination therapy (without VPA)	46 (16.2%)	VPA + lamotrigine	6 (14.6%)
VPA alone	0	VPA + levetiracetam	12 (29.3%)
VPA + 1 other ASM	5 (6.8%)	VPA + gabapentin	5 (12.2%)
VPA + 2 other ASMs	1 (1.4%)	VPA + carbamazepine	6 (14.6%)
VPA + ≥3 other ASMs	0	VPA + 1 other ASM	12 (29.3%)
≥ 1 month without any ASM, n (%)	**27 (36.5%)**	VPA + 2 other ASMs	6 (14.6%)
		VPA + ≥3 other ASMs	0
		≥ 1 month without any ASM, n (%)	**29 (70.7%)**
Cluster 3 Principally 2 ASMs (without VPA)	N = 28 (7.8%)	Cluster 8 Miscellanoeus	N = 54 (15.1%)
At least one ASM delivered		**At least one ASM delivered**	
Monotherapy (without VPA)	8 (28.6%)	Monotherapy (without VPA)	18 (33.3%)
Dual therapy (without VPA)	28 (100%)	Dual therapy (without VPA)	9 (16.7%)
Lamotrigine + levetiracetam	7 (25.0%)	Combination therapy (without VPA)	4 (7.4%)
Levatiracetam + zonisamide	4(14.3%)	VPA alone	23 (42.6)
Levatiracetam + pregabalin	3(10.7%)	VPA + 1 other ASM	20 (37.0%)
Other pairings of ASMs	17 (80.7%)	VPA + 2 other ASMs	10 (18.5%)
Combination therapy (without VPA)	6 (21.4%)	VPA + ≥3 other ASMs	0
VPA alone	0	**≥ 1 month without any ASM, n (%)**	**47 (87.0%)**
VPA + 1 other ASM	0		
VPA + 2 other ASMs	1 (3.6%)		
VPA + ≥3 other ASMs	0		
≥ 1 month without any ASM, n (%)	**2 (7.1%)**		

ASM: antiseizure medication; CPRD, Clinical Practice Research Datalink; VPA: valproate.
The treatment indicated in blue is the modal treatment for the cluster.

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Online Resource Table S3. Baseline characteristics according to treatment pattern

SNDS								
	CLUSTER 1 No ASM	**CLUSTER 2 1 ASM / No VPA**	**CLUSTER 3 2 ASMs / No VPA**	**CLUSTER 4 ≥3 ASMs / No VPA**	**CLUSTER 5 VPA alone**	**CLUSTER 6 VPA + 1 ASM**	**CLUSTER 7 VPA + ≥3 ASMs**	**TOTAL**
	N = 2,036	N = 1,871	N = 737	N = 297	N = 1,286	N = 760	N = 358	N = 7,345
Age at index date (years; median [IQR])	29 [18 ; 41]	29 [19 ; 38]	30 [22 ; 39]	31 [25 ; 40]	37 [23 ; 44]	32.5 [22 ; 42]	34 [22 ; 43]	31 [20 ; 41]
≥1 clinical relapse[1]	215 (10.6%)	244 (13.0%)	144 (19.5%)	94 (31.6%)	89 (6.9%)	85 (11.2%)	77 (21.5%)	948 (12.9%)
Number per woman (mean ± SD)	1.7 ± 1.8	1.4 ± 1.0	1.6 ± 1.4	2.5 ± 4.6	1.2 ± 0.7	1.5 ± 0.9	2.5 ± 3.8	1.7 ± 2.2
≥1 sick leave allowance	246 (12.1%)	321 (17.2%)	143 (19.4%)	56 (18.9%)	191 (14.9%)	125 (16.4%)	39 (10.9%)	1,121 (15.3%)
Obstetrical and gynaecological history								
Current contraceptive use	599 (29.4%)	734 (39.2%)	270 (36.6%)	94 (31.6%)	442 (34.4%)	261 (34.3%)	84 (23.5%)	2,484 (33.8%)
Contraceptive use in previous 5 years	879 (43.2%)	997 (53.3%)	392 (53.2%)	144 (48.5%)	618 (48.1%)	372 (48.9%)	125 (34.9%)	3,527 (48.0%)
Delivery of folic acid	127 (6.2%)	214 (11.4%)	86 (11.7%)	20 (6.7%)	77 (6.0%)	58 (7.6%)	31 (8.7%)	613 (8.3%)
Gynaecologist medical visit	479 (23.5%)	506 (27.0%)	207 (28.1%)	69 (23.2%)	316 (24.6%)	182 (23.9%)	71 (19.8%)	1,830 (24.9%)
Completed episode(s) of pregnancy[2]	18 (0.9%)	21 (1.1%)	≤10	≤10	13 (1.0%)	≤10	≤10	77 (1.0%)
Ongoing pregnancy at index date	33 (1.6%)	56 (3.0%)	24 (3.3%)	≤10	13 (1.0%)	≤10	≤10	147 (2.0%)

CPRD								
	CLUSTER 1 No ASM	**CLUSTER 2 1 ASM / No VPA**	**CLUSTER 3 2 ASMs / No VPA**		**CLUSTER 5 VPA alone**	**CLUSTER 6 VPA + 1 ASM**	**CLUSTER 8 Miscellaneous**	**TOTAL**
	N = 75	N = 74	N = 28	-	N = 86	N = 41	N = 54	N = 358
Age at index date (years; median [IQR])	30 [15 ; 41]	27 [18 ; 38]	29.5 [23.5 ; 36]		36 [20 ; 43]	37 [27 ; 44]	25 [17 ; 35]	30 [19 ; 41]
	N = 21	N = 21	N = 6		N = 26	N = 11	N = 24	N = 82
≥1 clinical relapse	4 (19.0%)	10 (47.6%)	2 (33.3%)		3 (11.5%)	7 (63.6%)	5 (20.8%)	31 (28.4%)
Number per woman (mean ± SD)	1.3 ± 0.5	1.9 ± 1.6	1.5 ± 0.7		1.0 ± 0.0	3.3 ± 3.5	2.6 ± 1.9	2.1 ± 2.1
≥1 sick leave allowance	246 (12.1%)	321 (17.2%)	143 (19.4%)		191 (14.9%)	125 (16.4%)	39 (10.9%)	1,121 (15.3%)
Obstetrical and gynaecological history								
Current contraceptive use	13 (17.3%)	30 (40.5%)	12 (42.9%)		27 (31.4%)	11 (26.8%)	14 (25.9%)	107 (29.9%)

Delivery of folic acid	7 (9.3%)	18 (24.3%)	5 (17.9%)	7 (8.1%)	7 (17.1%)	7 (13.0%)	51 (14.2%)
Gynaecologist medical visit	7 (9.3%)	9 (12.2%)	1 (3.6%)	6 (7.0%)	2 (4.9%)	3 (5.6%)	28 (7.8%)
Completed episode (s) of pregnancy[2]	1 (1.3%)	2 (2.7%)	0 (0.0%)	1 (1.2%)	1 (2.4%)	1 (1.9%)	6 (1.7%)
Ongoing pregnancy at index date	1 (1.3%)	6 (8.1%)	0 (0.0%)	3 (3.5%)	0 (0.0%)	1 (1.9%)	11 (3.1%)

[1] Clinical relapse defined by at least one ED visit or hospitalisation for epilepsy.

[2] Last pregnancy prior to the index date

ASM: antiseizure medication; ED: emergency department; IQR: interquartile range; SD: standard deviation.

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Online Resource Table S4. Antiseizure medication treatments in the ninety days prior to valproate discontinuation

SNDS								
	CLUSTER 1 No ASM	**CLUSTER 2 1 ASM / No VPA**	**CLUSTER 3 2 ASMs / No VPA**	**CLUSTER 4 ≥3 ASMs / No VPA**	**CLUSTER 5 VPA alone**	**CLUSTER 6 VPA + 1 ASM**	**CLUSTER 7 VPA + ≥3 ASMs**	**TOTAL**
	N = 2,036	N = 1,871	N = 737	N = 297	N = 1,286	N = 760	N = 358	N = 7,345
Final valproate dose (mg/day; mean ± SD)	998 ± 721	774 ± 452	805 ± 464	804 ± 428	1172 ± 668	1157 ± 644	1336 ± 881	977 ± 644
Use of taper prior to discontinuation (n, %)	479 (23.5%)	738 (39.4%)	302 (41.0%)	120 (40.4%)	139 (10.8%)	112 (14.7%)	59 (16.5%)	1,949 (26.5%)
MPR >80% (previous year)	771 (37.9%)	980 (52.4%)	450 (61.1%)	194 (65.3%)	370 (28.8%)	303 (39.9%)	189 (52.8%)	3,257 (44.3%)
Valproate monotherapy	1,385 (68.0%)	174 (9.3%)	≤10	≤10	1,162 (90.4%)	32 (4.2%)	≤10	2,769 (37.7%)
Valproate + 1 other ASM	419 (20.6%)	1,493 (79.8%)	119 (16.1%)	16 (5.4%)	111 (8.6%)	637 (83.8%)	31 (8.7%)	2,826 (38.5%)
Valproate + lamotrigine	124 (6.1%)	713 (38.1%)	51 (6.9%)	≤10	26 (2.0%)	215 (28.3%)	11 (3.1%)	1,144 (15.6%)
Valproate + levetiracetam	84 (4.1%)	497 (26.6%)	31 (4.2%)	≤10	19 (1.5%)	120 (15.8%)	≤10	761 (10.4%)
Valproate + clobazepam	63 (3.1%)	45 (2.4%)	11 (1.5%)	≤10	29 (2.3%)	82 (10.8%)	≤10	238 (3.2%)
Valproate + 2 other ASMs	150 (7.4%)	178 (9.5%)	530 (71.9%)	67 (22.6%)	13 (1.0%)	80 (10.5%)	251 (70.1%)	1,269 (17.3%)
Valproate + 3 or more other ASMs	82 (4.0%)	26 (1.4%)	80 (10.9%)	213 (71.7%)	0 (0.0%)	11 (1.4%)	69 (19.3%)	481 (6.5%)
CPRD								
	CLUSTER 1 No ASM	**CLUSTER 2 1 ASM / No VPA**	**CLUSTER 3 2 ASMs / No VPA**		**CLUSTER 5 VPA alone**	**CLUSTER 6 VPA + 1 ASM**	**CLUSTER 8 Miscellaneous**	**TOTAL**
	N = 75	N = 74	N = 28	-	N = 86	N = 41	N = 54	N = 358
Final valproate dose (mg/day; mean ± SD)	831 ± 488	890 ± 575	656 ± 260		916 ± 462	1174 ± 615	962 ± 520	927 ± 522
Use of taper prior to discontinuation (n, %)	2/46 (4.3%)	7/33 (21.2%)	3/9 (33.3%)		1/66 (1.5%)	2/28 (7.1%)	1/35 (2.9%)	16/217 (7.4%)
MPR >80% (previous year)	51 (68.0%)	56 (75.7%)	18 (64.3%)		53 (61.6%)	20 (48.8%)	36 (66.7%)	234 (65.4%)
Valproate monotherapy	64 (85.3%)	7 (9.5%)	0 (0.0%)		86 (100.0%)	5 (12.2%)	27 (50.0%)	189 (52.8%)
Valproate + 1 other ASM	8 (10.7%)	63 (85.1%)	3 (10.7%)		0 (0.0%)	31 (75.6%)	14 (25.9%)	119 (33.2%)
Valproate + lamotrigine	3 (4.0%)	20 (27.0%)	0 (0.0%)		0 (0.0%)	6 (14.6%)	5 (9.3%)	34 (9.5%)

Valproate + levetiracetam	4 (5.3%)	33 (44.6%)	2 (7.1%)	0 (0.0%)	9 (22.0%)	5 (9.3%)	53 (14.8%)
Valproate + carbamazepine	1 (1.3%)	3 (4.1%)	1 (3.6%)	0 (0.0%)	6 (14.6%)	0 (0.0%)	11 (3.1%)
Valproate + gabapentin	0 (0.0%)	4 (5.4%)	0 (0.0%)	0 (0.0%)	3 (7.3%)	0 (0.0%)	7 (2.0%)
Valproate + topiramate	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	2 (3.7%)	4 (1.1%)
Valproate + 2 other ASMs	3 (4.0%)	4 (5.4%)	23 (82.1%)	0 (0.0%)	3 (7.3%)	9 (16.7%)	42 (11.7%)
Valproate + 3 or more other ASMs	0 (0.0%)	0 (0.0%)	2 (7.1%)	0 (0.0%)	2 (4.9%)	4 (7.4%)	8 (2.2%)

ASM: antiseizure medication; IQR: interquartile range; MPR: medication possession ratio; SD: standard deviation.

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Online Resource Table S5. Variables associated with valproate re-use pattern (SNDS cohort: multivariate analysis)

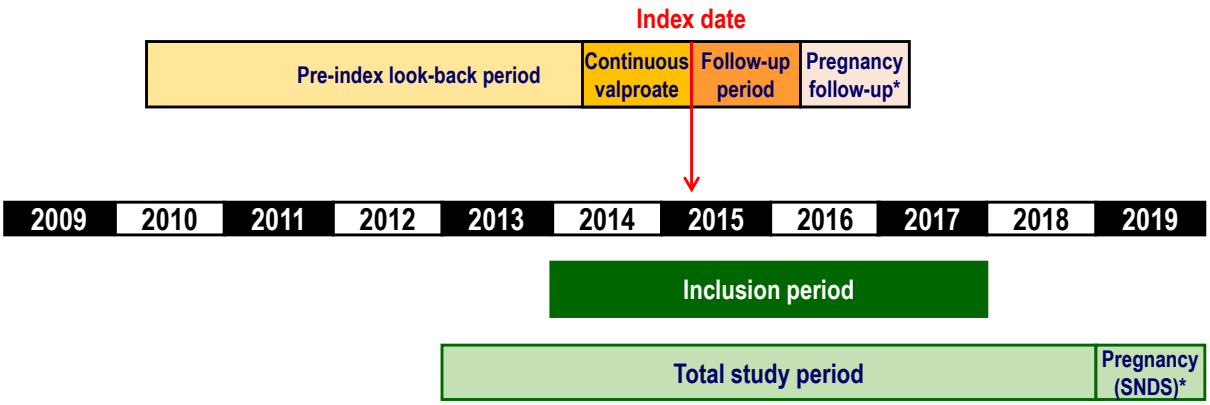
	GROUP A (Cluster 2-4) **Other ASMs n = 2,905**	**GROUP B** (Cluster 1) **No ASMs n = 2,036**	**GROUP C** (Cluster 5) **VPA alone n = 1,286**	**GROUP D** (Cluster 6 & 7) **VPA + ASMs n = 1,118**	**GROUP A vs. GROUP D**	**GROUP B vs. GROUP D**	**GROUP C vs. GROUP D**	**p-value**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**OR [95% CI] n = 2,905 vs. 1,118**	**OR [95% CI] n = 2,036 vs. 1,118**	**OR [95% CI] n = 1,286 vs. 1,118**	
Epilepsy care during the 90-day pre-index period								<0.0001
None	945 (32.5%)	1,368 (67.2%)	1,028 (79.9%)	727 (65.0%)	1	1	1	
EEG +/- MRI alone	503 (17.3%)	252 (12.4%)	67 (5.2%)	92 (8.2%)	**2.81 [2.13 ; 3.70]**	**1.89 [1.38 ; 2.59]**	0.91 [0.61 ; 1.35]	
Neurologist/psychiatrist consultations alone	1,042 (35.9%)	301 (14.8%)	152 (11.8%)	229 (20.5%)	**2.66 [2.18 ; 3.26]**	1.13 [0.89 ; 1.45]	0.89 [0.67 ; 1.19]	
EEG +/- MRI + Neurologist/psychiatrist consultations	415 (14.3%)	115 (5.6%)	39 (3.0%)	70 (6.3%)	**3.08 [2.27 ; 4.18]**	**1.48 [1.02 ; 2.16]**	0.85 [0.53 ; 1.37]	
Number of ASMs delivered during the 90-day pre-index period								<0.0001
<4	442 (15.2%)	1,432 (70.3%)	1,128 (87.7%)	108 (9.7%)	1	1	1	
[4-5]	1,001 (34.5%)	293 (14.4%)	126 (9.8%)	373 (33.4%)	**0.18 [0.14 ; 0.25]**	**0.10 [0.08 ; 0.13]**	**0.07 [0.05 ; 0.09]**	
>5	1,462 (50.3%)	311 (15.3%)	32 (2.5%)	637 (57.0%)	**0.12 [0.09 ; 0.17]**	**0.08 [0.06 ; 0.11]**	**0.02 [0.01 ; 0.02]**	
VPA dose-tapering phase during the 1-year pre-index period								<0.0001
No	1,745 (60.1%)	1,557 (76.5%)	1,147 (89.2%)	947 (84.7%)	1	1	1	
Yes	1,160 (39.9%)	479 (23.5%)	139 (10.8%)	171 (15.3%)	**2.54 [2.07 ; 3.10]**	**2.30 [1.80 ; 2.94]**	1.03 [0.77 ; 1.38]	
ASM treatment pattern								<0.0001
Non-exposed within the 3 months after the index date	91 (3.1%)	1,816 (89.2%)	1,106 (86.0%)	472 (42.2%)	**0.05 [0.04 ; 0.07]**	**4.22 [3.24 ; 5.50]**	**1.75 [1.30 ; 2.36]**	
Same treatment in the month before and after the index date	1,909 (65.7%)	78 (3.8%)	39 (3.0%)	410 (36.7%)	**1.41 [1.15 ; 1.72]**	**0.52 [0.37 ; 0.73]**	0.77 [0.49 ; 1.19]	
Other	905 (31.2%)	142 (7.0%)	141 (11.0%)	236 (21.1%)	1	1	1	
Current pregnancy at index date								0.0167
No	2,815 (96.9%)	2,003 (98.4%)	1,273 (99.0%)	1,107 (99.0%)	1	1	1	
Yes	90 (3.1%)	33 (1.6%)	13 (1.0%)	11 (1.0%)	**2.12 [1.08 ; 4.14]**	**3.12 [1.40 ; 6.96]**	1.59 [0.62 ; 4.10]	
ASMs delivered during the 90-day pre-index period								
Lamotrigine (ref: not delivered)	1353 (46.6%)	223 (11.0%)	31 (2.4%)	404 (36.1%)	**1.42 [1.17 ; 1.72]**	0.82 [0.64 ; 1.04]	**0.23 [0.15 ; 0.35]**	<0.0001
Levetiracetam (ref: not delivered)	1040 (35.8%)	160 (7.9%)	23 (1.8%)	253 (22.6%)	**1.66 [1.35 ; 2.03]**	0.86 [0.66 ; 1.11]	**0.23 [0.15 ; 0.37]**	<0.0001

	GROUP A (Cluster 2-4) **Other ASMs n = 2,905**	**GROUP B** (Cluster 1) **No ASMs n = 2,036**	**GROUP C** (Cluster 5) **VPA alone n = 1,286**	**GROUP D** (Cluster 6 & 7) **VPA + ASMs n = 1,118**	**GROUP A vs. GROUP D**	**GROUP B vs. GROUP D**	**GROUP C vs. GROUP D**	**p-value**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**OR [95% CI] n = 2,905 vs. 1,118**	**OR [95% CI] n = 2,036 vs. 1,118**	**OR [95% CI] n = 1,286 vs. 1,118**	
Clobazam (ref: not delivered)	565 (19.4%)	179 (8.8%)	38 (3.0%)	283 (25.3%)	0.91 [0.74 ; 1.12]	0.85 [0.66 ; 1.09]	**0.51 [0.34 ; 0.77]**	0.0138
VPA MPR during the 1-year pre-index period								<0.0001
]60% - 80%]	1281 (44.1%)	1265 (62.1%)	916 (71.2%)	626 (56.0%)	1	1	1	
>80%	1624 (55.9%)	771 (37.9%)	370 (28.8%)	492 (44.0%)	**1.74 [1.47 ; 2.05]**	1.07 [0.89 ; 1.29]	0.85 [0.68 ; 1.05]	
Age at index date (in years (in categories								<0.0001
[13-19]	687 (23.6%)	589 (28.9%)	234 (18.2%)	207 (18.5%)	1	1	1	
[20-29]	776 (26.7%)	451 (22.2%)	209 (16.3%)	272 (24.3%)	0.78 [0.60 ; 1.01]	1.18 [0.89 ; 1.56]	**1.52 [1.09 ; 2.12]**	
[30-39]	766 (26.4%)	400 (19.6%)	284 (22.1%)	250 (22.4%)	**0.70 [0.54 ; 0.91]**	0.98 [0.73 ; 1.31]	**1.75 [1.25 ; 2.45]**	
[40-49]	676 (23.3%)	596 (29.3%)	559 (43.5%)	389 (34.8%)	**0.51 [0.39 ; 0.66]**	0.76 [0.58 ; 1.00]	**1.80 [1.32 ; 2.47]**	
History of epilepsy within the 5-year pre-index period								<0.0001
<1 year	297 (10.2%)	223 (11.0%)	112 (8.7%)	77 (6.9%)	1	1	1	
[1-4] years	1064 (36.6%)	918 (45.1%)	578 (44.9%)	338 (30.2%)	0.93 [0.66 ; 1.30]	0.86 [0.60 ; 1.24]	1.10 [0.73 ; 1.66]	
]4-5[years	499 (17.2%)	354 (17.4%)	236 (18.4%)	198 (17.7%)	0.73 [0.51 ; 1.05]	0.74 [0.50 ; 1.09]	1.02 [0.66 ; 1.60]	
≥5 years	1045 (36.0%)	541 (26.6%)	360 (28.0%)	505 (45.2%)	**0.64 [0.46 ; 0.90]**	**0.51 [0.36 ; 0.74]**	0.73 [0.48 ; 1.11]	
Comorbidities during the 1-year pre-index period								
Paraplegia (ref: none)	24 (0.8%)	38 (1.9%)	20 (1.6%)	37 (3.3%)	**0.28 [0.15 ; 0.53]**	0.69 [0.39 ; 1.23]	0.69 [0.34 ; 1.40]	0.0014
Mental impairment (ref: none)	186 (6.4%)	220 (10.8%)	103 (8.0%)	147 (13.1%)	**0.57 [0.42 ; 0.77]**	0.99 [0.73 ; 1.33]	0.85 [0.60 ; 1.22]	0.0016
Psychiatric disorders starting in childhood (ref: none)	62 (2.1%)	98 (4.8%)	47 (3.7%)	32 (2.9%)	0.77 [0.46 ; 1.29]	**2.01 [1.22 ; 3.33]**	**2.16 [1.21 ; 3.85]**	0.0016
Neurotic and mood disorders (ref: none)	199 (6.9%)	281 (13.8%)	152 (11.8%)	120 (10.7%)	0.77 [0.56 ; 1.06]	1.22 [0.88 ; 1.69]	0.93 [0.64 ; 1.35]	0.0334
Other psychiatric disorders* (ref: none)	160 (5.5%)	180 (8.8%)	91 (7.1%)	67 (6.0%)	1.47[1.01;2.14]	1.25[0.85;1.84]	0.95[0.61;1.46]	0.0569
Other neurological conditions** (ref: none)	75 (2.6%)	84 (4.1%)	40 (3.1%)	61 (5.5%)	**0.55[0.36;0.85]**	0.89[0.58;1.36]	0.86[0.51;1.44]	0.0639
Number of consultations (neurologist/psychiatrist excluded during the 90-day pre-index period								0.0934
0	505 (17.4%)	455 (22.3%)	290 (22.6%)	251 (22.5%)	1	1	1	
1	653 (22.5%)	474 (23.3%)	294 (22.9%)	255 (22.8%)	1.26[0.98;1.63]	0.96[0.73;1.25]	0.87[0.64;1.19]	
[2-3]	939 (32.3%)	598 (29.4%)	372 (28.9%)	344 (30.8%)	1.27[0.99;1.62]	0.94[0.72;1.22]	0.93[0.69;1.25]	
>3	808 (27.8%)	509 (25.0%)	330 (25.7%)	268 (24.0%)	**1.59[1.21;2.09]**	1.08[0.81;1.44]	1.11[0.80;1.54]	

	GROUP A (Cluster 2-4) **Other ASMs n = 2,905**	**GROUP B** (Cluster 1) **No ASMs n = 2,036**	**GROUP C** (Cluster 5) **VPA alone n = 1,286**	**GROUP D** (Cluster 6 & 7) **VPA + ASMs n = 1,118**	**GROUP A vs. GROUP D**	**GROUP B vs. GROUP D**	**GROUP C vs. GROUP D**	**p-value**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**OR [95% CI] n = 2,905 vs. 1,118**	**OR [95% CI] n = 2,036 vs. 1,118**	**OR [95% CI] n = 1,286 vs. 1,118**	
Number of other CNS drugs delivered during the 90-day pre-index period								0.0654
0	1301 (44.8%)	762 (37.4%)	483 (37.6%)	435 (38.9%)	1	1	1	
1	597 (20.6%)	360 (17.7%)	224 (17.4%)	186 (16.6%)	0.94[0.74;1.19]	1.18[0.91;1.55]	1.10[0.81;1.49]	
[2-3]	464 (16.0%)	340 (16.7%)	213 (16.6%)	221 (19.8%)	0.80[0.62;1.02]	1.05[0.80;1.37]	0.90[0.66;1.23]	
>3	543 (18.7%)	574 (28.2%)	366 (28.5%)	276 (24.7%)	0.87[0.67;1.12]	**1.45[1.10;1.93]**	1.18[0.86;1.62]	

ASM: antiseizure medication; CI: confidence interval; CNS: central nervous system;: *Système National des Données de Santé,* VPA: valproate.
* Other psychiatric disorders: psychiatric disorders other than Psychotic disorders, Neurotic and mood disorders, Mental impairment, Addictive disorders, Psychiatric disorders beginning in childhood
** Other neurological conditions: neurological conditions other than Dementias, Parkinson's disease, Multiple sclerosis, Paraplegia, Myopathy or myasthenia gravis, Epilepsy
The model was further adjusted for having ≥1 hospitalisation related to epilepsy, the number of comorbidities, diabetes, and ≥1 record of contraceptive method.

Online Resource Figure S1. Study design

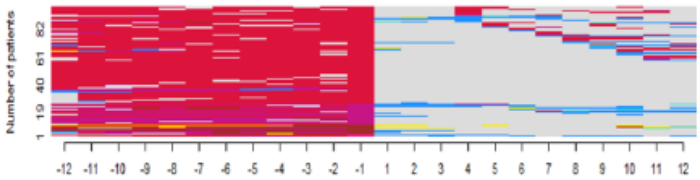


CPRD: Clinical Practice Research Datalink; SNDS: *Système National des Données de Santé.*
*For patients in the SNDS cohort, an extra year of follow-up was implemented to capture pregnancies, which are documented at delivery. This was not required for the CPRD, as pregnancies are documented in real time.

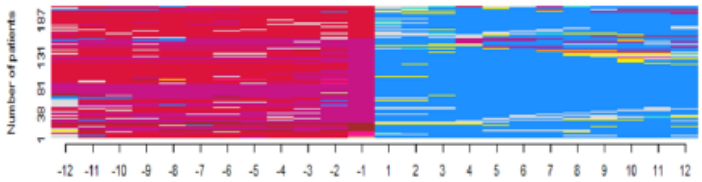
Online Resource Figure S2. Clusters of treatment sequence patterns in pregnant women (SNDS cohort, N = 513)

Clusters with a pattern of low valproate re-use **N = 440; 85.8%**

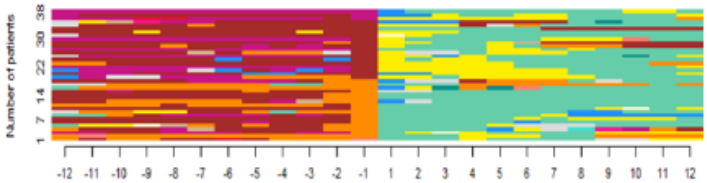
1. Principally no ASM at all
N = 99 (19.3%)



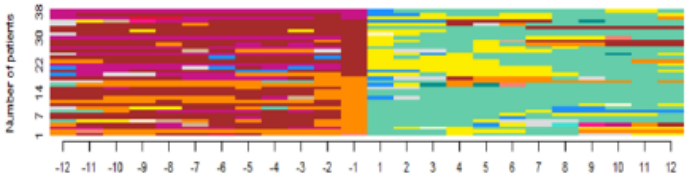
2. Principally 1 ASM (without VPA)
N = 209 (40.7%)



3. Principally 2 ASMs (without VPA)
N = 94 (18.3%)

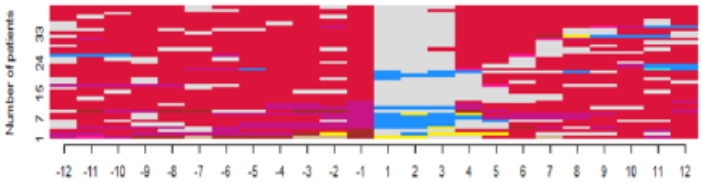


4. Principally ≥3 ASMs (without VPA)
N = 38 (7.4%)

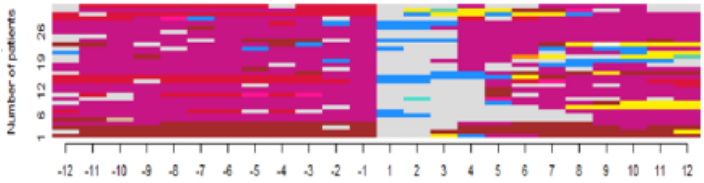


Clusters with a pattern of high valproate re-use **N = 73; 14.2%**

5. Principally VPA alone
N = 41 (8.0%)



6. Principally VPA and one other ASM
N = 32 (6.2%)



ASM: antiseizure medication; SNDS, *Système National des Données de Santé*; VPA: valproate.