Trends in gabapentinoid prescribing: an observational study in UK primary care using the Clinical Practice Research Datalink. Supplementary Materials

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Definitions

Practice migration

The GOLD dataset is the primary care records from practices using the Vision system for computerised records and AURUM is from the EMIS system. Although the information they contain is essentially the same, they are held separately as the formats are slightly different and the interfaces that the GPs use to create the data are different. Some practices have "migrated" their computer system from Vision to EMIS and therefore individuals registered with these practices appear in both datasets. To ensure that the datasets were mutually exclusive and allow valid meta-analysis, people from these migrator practices were removed from the GOLD dataset.

Incident prescriptions

An incident prescription was defined as the first in the CPRD record. We required this prescription to occur between 01/04/1997 (gabapentin) and 01/04/2004 (pregabalin) and 30/09/2019, but used the whole of the available record, which for some people beginnings before 1997, in the definition of incidence. Where more than one product was prescribed on the same date (e.g. gabapentin tablets in two different strengths), they were considered a single prescription.

Duration of treatment

Treatment period defined to end if no further prescription within 56 days

GOLD: merge with common dosages look up file

1. Create indicator if no prescription for 56 days (or no further prescription)
2. Therapy start date = first script date and new script date if no script for 56 days
3. Calculate script duration as numdays if available, or qty/daily_dose if not, for the last script in the treatment period or if more than 30 days between scripts
4. Calculate script duration as number of days between scripts if <=30 and >=7
5. If time between scripts is <7days then use numdays or qty/daily_dose for duration
6. Impute mean duration per patient per drug if missing or if >56
7. If still missing, impute mean duration per patient
8. If two scripts on the same day, replace the first numdays (currently 0) to be the same as the last script on that day
9. If two scripts within 7 days of each other for different prodcodes then used qty/ndd for script duration
10. If duration is still less than 7 days, replace as missing (likely prescribed alongside another drug)
11. Impute mean duration per patient per drug if missing
12. If still missing, use mean duration of overall prodcode specific mean
13. If still missing and within 7 days of another script use duration from that script
14. Generate end date of treatment period as the eventdate+duration for the last script in that period
15. If end of treatment period is within 56 days of the start of the next treatment period, then join treatment periods
16. Calculate total treatment duration as difference between treatment end date and treatment start date

AURUM: As above with GOLD, excluding using qty/daily_dose if numdays missing as daily_dose is not available in AURUM

Numeric daily dose

The numeric daily dose was the dose of the drug in mg that was estimated to have been prescribed for each day for the duration of a prescription. This was calculated differently in GOLD and in AURUM, according to the field available in the dataset.

GOLD

1. Generate numerical daily dose (ndd) as daily_dose*strength if not a capsule or tablet and less than 100 (but not 50)
2. Replace ndd as daily_dose if not a capsule or tablet but daily_dose>100 or =50
3. If it is a capsule or tablet then ndd = daily_dose, if daily_dose is >24
4. If a capsule or tablet and daily_dose<25 then ndd=daily_dose*strength
5. If missing, then use daily_dose=qty/treatment duration
6. If more than one script on the same day the sum the ndd and keep one script per person per day
7. Set upper and lower limits of possible daily doses based on BNF (300 – 4800 for gabapentin, 50-600 for pregabalin)
8. Calculate average daily dose for treatment period as mean of ndd in that period

AURUM:

As for GOLD, but more missing information on quantity and dose. Therefore,

1. Replace daily dose with 18000/duration_trt if unit==”pack” & ndd==.
2. Where quantity is missing or <1, replace with mean value for that product code for that person, if still missing replace with mean value for that product code overall.
3. Where duration_trt is missing or <1, replace with mean value for that product code for that person, if still missing replace with mean value for that product code overall.
4. Where strength is missing or <1, replace with mean value for that product code for that person, if still missing replace with mean value for that product code overall.

Co-prescriptions

Durations of treatment were calculated for prescriptions for all drugs considered in the study. Drugs were considered to be co-prescribed with gabapentioids where the estimated treatments periods (start and end dates) of the gabapentinoid and potentially interacting drug overlapped. First and later treatment periods were included in this definition.

Licensed indications

Licensed indications were neuropathic pain, epilepsy and anxiety (pregabalin only). Licensed indications defined by a clinical code for these conditions before the end of an individual’s final treatment period.

Unlicensed indications

Unlicensed indications were fibromyalgia, chronic back pain (without radiculopathy), chronic neck pain, osteoarthritis, chronic headache, migraine, chronic abdominal pain and restless legs syndrome. They were initially defined by a clinical code for these conditions in the period 14 days before to 90 days after incident gabapentinoid prescription. In a sensitivity analysis, this period was widened to 30 days before to 90 days after the incident gabapentinoid prescription.

Prescribing pathway

Drugs on the prescribing pathway were opioids, benzodiazepines, Z-drug hypnotics (zopiclone and zolpidem), and antidepressants. Prescribing of these drugs was considered in the 12 months prior to the incident gabapentinoid prescription. All individuals were required to have 12 months of up-to-standard (CPRD's marking of quality) data before the incident gabapentinoid prescription.

Mid-year population for prevalence calculations

Both the GOLD and AURUM datasets are provided with a "Denominator file" that includes the ID number and the start and end registration dates of all individuals ever included in the dataset. We used this to calculate the period for which individuals were at risk of a prescription. The mid-year population estimates were the number of people (aged ≤18 years) contributing to the dataset on 1st July each year (i.e. where 1st July in a given year fell between their start and end dates) was considered the mid-year population.

Joinpoint Analysis

Joinpoint selects the final model using two different methods: Permutation Test and Bayesian Information Criterion (BIC). However, the Joinpoint software uses a sequence of permutation tests to select the final model as a default method. Each one of the permutation tests performs a test of the null hypothesis H_0: number of joinpoints = k_a against the alternative H_a: number of joinpoints = k_b where $K_a < K_b$. The procedure begins with k_a = MIN and k_b = MAX. If the null is rejected, then increase k_a by 1; otherwise, decrease k_b by 1. The procedure continues until $k_a = k_b$ and the final value of is the selected number of joinpoints.

Year	AURUM		GOLD		Combined	
	Gabapentin	Pregabalin	Gabapentin	Pregabalin	Gabapentin	Pregabalin
	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
1997-98	5.98 (5.37, 6.65)	--	7.63 (6.22, 9.35)	--	6.30 (5.73, 6.92)	--
1998-99	12.51 (11.64, 13.45)	--	16.14 (14.16, 18.38)	--	13.28 (12.47, 14.15)	--
1999-00	31.91 (30.52, 33.37)	--	43.63 (40.63, 46.85)	--	34.84 (33.55, 36.18)	--
2000-01	57.35 (55.50, 59.27)	--	78.32 (74.59, 82.23)	--	63.21 (61.51, 64.96)	--
2001-02	85.21 (82.98, 87.51)	--	116.53 (112.31, 120.90)	--	94.86 (92.83, 96.93)	--
2002-03	120.80 (118.16, 123.50)	--	160.83 (156.24, 165.57)	--	134.22 (131.88,136.60)	--
2003-04	150.43 (147.50, 153.41)	--	205.62 (200.76, 210.60)	--	170.58 (168.01, 173.19)	--
2004-05	163.84 (160.81, 166.93)	57.30 (55.52, 59.13)	231.78 (226.83, 236.84)	84.93 (81.97, 88.00)	190.05 (187.39, 192.76)	68.15 (66.57, 69.78)
2005-06	168.29 (165.24, 171.40)	118.17 (115.63, 120.77)	236.13 (231.20, 241.16)	158.58 (154.57, 162.69)	194.64 (191.97, 197.35)	133.68 (131.48, 135.91)
2006-07	176.28 (173.18, 179.43)	124.78 (122.18, 127.42)	264.27 (259.10, 269.53)	157.16 (153.21, 161.21)	211.23 (208.47, 214.04)	136.99 (134.79, 139.23)
2007-08	212.91 (209.53, 216.35)	128.00 (125.39, 130.66)	310.01 (304.48, 315.64)	158.29 (154.38, 162.30)	251.38 (248.39, 254.40)	139.44 (137.25, 141.68)
2008-09	249.78 (246.13, 253.48)	152.96 (150.13, 155.85)	350.98 (345.15, 356.91)	197.27 (192.93, 201.70)	289.61 (286.43, 292.83)	170.00 (167.59, 172.45)
2009-10	294.98 (291.03, 298.97)	186.51 (183.40, 189.68)	383.55 (377.51, 389.70)	255.70 (250.80, 260.69)	329.18 (325.81, 332.58)	213.71 (211.01, 216.44)
2010-11	337.38 (333.18, 341.63)	229.63 (226.19, 233.13)	410.18 (403.97, 416.48)	287.41 (282.26, 292.66)	365.01 (361.49, 368.56)	251.82 (248.91, 254.75)
2011-12	419.19 (414.52, 423.91)	236.75 (233.26, 240.28)	484.02 (477.32, 490.81)	279.09 (274.05, 284.22)	443.51 (439.66, 447.40)	252.77 (249.88, 255.69)
2012-13	469.30 (464.39, 474.27)	259.59 (255.95, 263.27)	525.05 (518.13, 532.08)	298.13 (292.96, 303.39)	490.09 (486.06, 494.15)	274.14 (271.15, 277.17)
2013-14	559.70 (554.28, 565.18)	292.72 (288.82, 296.66)	564.39 (557.25, 571.61)	317.50 (312.20, 322.88)	561.43 (557.10, 565.78)	302.10 (298.95, 305.28)
2014-15	609.51 (603.87, 615.20)	307.28 (303.32, 311.30)	569.61 (562.50, 576.81)	313.48 (308.26, 318.78)	595.08 (590.65, 599.54)	309.59 (306.42, 312.78)
2015-16	644.70 (638.93, 650.51)	326.29 (322.23, 330.39)	545.87 (538.95, 552.88)	300.08 (295.01, 305.23)	610.10 (605.63, 614.60)	316.87 (313.69, 320.08)
2016-17	684.52 (678.63, 690.46)	345.10 (340.97, 349.27)	504.45 (497.83, 511.15)	270.89 (266.11, 275.76)	624.57 (620.07, 629.10)	319.87 (316.70, 323.08)
2017-18	624.49 (618.92, 630.12)	361.13 (356.94, 365.36)	442.58 (436.42, 448.81)	263.05 (258.37, 267.82)	564.92 (560.67, 569.20)	328.74 (325.54, 331.97)
2018-19	540.39 (535.23, 545.60)	363.62 (359.43, 367.86)	356.34 (350.85, 361.90)	244.32 (239.84, 248.89)	481.52 (477.61, 485.47)	325.11 (321.93, 328.32)
2019	463.99 (457.20, 470.88)	333.75 (325.51, 342.21)	265.53 (258.89, 272.34)	193.92 (185.85, 202.34)	402.87 (397.77, 408.03)	290.26 (284.07, 296.58)

Supplementary Table 1: Annual incidence rate of first gabapentinoid prescriptions (per 100,000 patient years) 1997 – 2019 resulting from meta-analysis of CPRD GOLD and AURUM data

Supplementary Table 2. Annual prevalence rate of gabapentinoid prescriptions (per 100,000 patient years) 1997 – 2019 resulting from meta-analysis of CPRD GOLD and AURUM data

Year	AURUM		GOLD		Combined	
	Gabapentin	Pregabalin	Gabapentin	Pregabalin	Gabapentin	Pregabalin
	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)	Rate (95% CI)
1997-98	11.16 910.32, 12.07)	--	12.80 (10.91, 15.01)	--	11.42 (10.61, 12.22)	--
1998-99	35.27 (33.78, 36.83)	--	38.79 (35.57, 42.31)	--	35.87 (34.48, 37.26)	--
1999-00	108.24 (105.64, 110.9)	--	119.16 (113.97, 124.59)	--	110.39 (108.04, 112.75)	--
2000-01	239.78 (235.95, 243.67)	--	263.10 (256.08, 270.31)	--	245.09 (241.7, 248.48)	--
2001-02	436.11 (431.00, 441.28)	--	479.12 (470.24, 488.16)	--	446.76 (442.3, 451.22)	--
2002-03	692.74 (686.38, 699.17)	--	718.87 (708.96, 728.91)	--	700.36 (694.98, 705.74)	--
2003-04	1018.59 (1010.96, 1026.28)	--	1037.81 (1026.67, 1049.06)	--	1024.72 (1018.4, 1031.05)	--
2004-05	1346.99 (1338.30, 1355.74)	--	1394.36 (1382.19, 1406.64)	--	1362.96 (1355.86, 1370.06)	--
2005-06	1646.10 (1636.57, 1655.69)	252.25 (248.51, 517.38)	1775.21 (1761.73, 1788.79)	330.55 (324.72, 336.48)	1689.09 (1681.28, 1696.90)	275.04 (271.87, 278.22)
2006-07	1927.28 (1917.07, 1937.54)	512.04 (506.75, 753.09)	2178.88 (2164.14, 2193.72)	617.07 (609.18, 625.05)	2008.76 (2000.34, 2017.18)	544.57 (540.15, 548.98)
2007-08	2275.94 (2264.95, 2286.99)	746.70 (740.36, 995.43)	2628.74 (2612.75, 2644.82)	867.81 (858.56, 877.15)	2389.09 (2380.01, 2398.18)	785.32 (780.07, 790.56)
2008-09	2650.45 (2638.70, 2662.26)	988.15 (980.93, 1279.80)	3078.17 (3061.12, 3095.30)	1120.10 (1109.73, 1130.56)	2788.17 (2778.48, 2797.87)	1031.25 (1025.30, 1037.20)
2009-10	3094.22 (3081.61, 3106.88)	1271.60 (1263.45, 1609.18)	3564.7 93546.60, 3582.90)	1437.02 (1425.42, 1448.72)	3247.75 (3237.38, 3258.12)	1326.17 (1319.47, 1332.86)
2010-11	3577.12 (3563.69, 3590.60)	1600.06 (1590.99, 1947.32)	4030.23 (4011.21, 4049.34)	1822.96 (1810.03, 1835.97)	3727.74 (3716.75, 3738.74)	1673.48 (1666.04, 1680.93)
2011-12	4166.57 (4152.18, 4181.01)	1937.35 (1927.43, 2274.04)	4539.16 (4519.17, 4559.23)	2146.60 (2132.70, 2160.58)	4293.72 (4282.02, 4305.42)	2007.88 (1999.79, 2015.98)
2012-13	4808.58 (4793.28, 4823.94)	2263.35 (2252.72, 2661.14)	5065.97 (5045.10, 5086.93)	2429.98 (2415.34, 2444.71)	4898.53 (4886.17, 4910.89)	2320.83 (2312.21, 2329.46)
2013-14	5606.15 (5589.59, 5622.77)	2649.53 (2637.97, 3001.84)	5549.44 (5527.84, 5571.12)	2701.79 (2686.51, 2717.16)	5585.16 (5571.99, 5598.32)	2668.53 (2659.29, 2677.77)
2014-15	6316.55 (6299.09, 6334.06)	2989.58 (2977.36, 3272.71)	5874.10 (5852.14, 5896.14)	2920.54 (2904.83, 2936.34)	6145.30 (6131.61, 6158.99)	2963.60 (2953.93, 2973.26)
2015-16	6934.99 (6916.91, 6953.11)	3260.04 (3247.41, 3524.77)	6115.29 (6093.11, 6137.54)	3044.55 (3028.66, 3060.52)	6607.98 (6593.95, 6622.01)	3176.68 (3166.78, 3186.59)
2016-17	7439.18 (7420.69, 7457.72)	3511.76 (3498.80, 3725.63)	6127.18 (6105.10, 6149.33)	3089.71 (3073.79, 3105.70)	6898.52 (6884.32, 6912.71)	3343.56 (3333.49, 3353.63)
2017-18	7777.84 (7759.17, 7796.55)	3712.41 (3699.24, 3896.24)	6040.80 (6019.07, 6062.61)	3047.98 (3032.31, 3063.73)	7040.68 (7026.50, 7054.86)	3437.52 (3427.42, 3447.63)
2018-19	7898.15 (7879.51, 7916.83)	3882.85 (3869.50, 3936.33)	5869.80 (5848.48, 5891.19)	3063.55 (3047.94, 3079.25)	7019.75 (7005.69, 7033.80)	3537.37 (3527.20, 3547.54)
2019	7806.03 (7787.44, 7824.66)	3922.85 (3909.40, 3936.33)	5595.16 (5574.47, 5615.92)	2980.54 (2965.24, 2995.91)	6818.99 (6805.14, 6832.84)	3512.45 (3502.34, 3522.57)

Supplementary Table 3. Incidence of first gabapentinoid prescriptions (per 100,000 patient years), by age group and sex, 1997- 2019, resulting from meta-analysis of CPRD GOLD and AURUM data

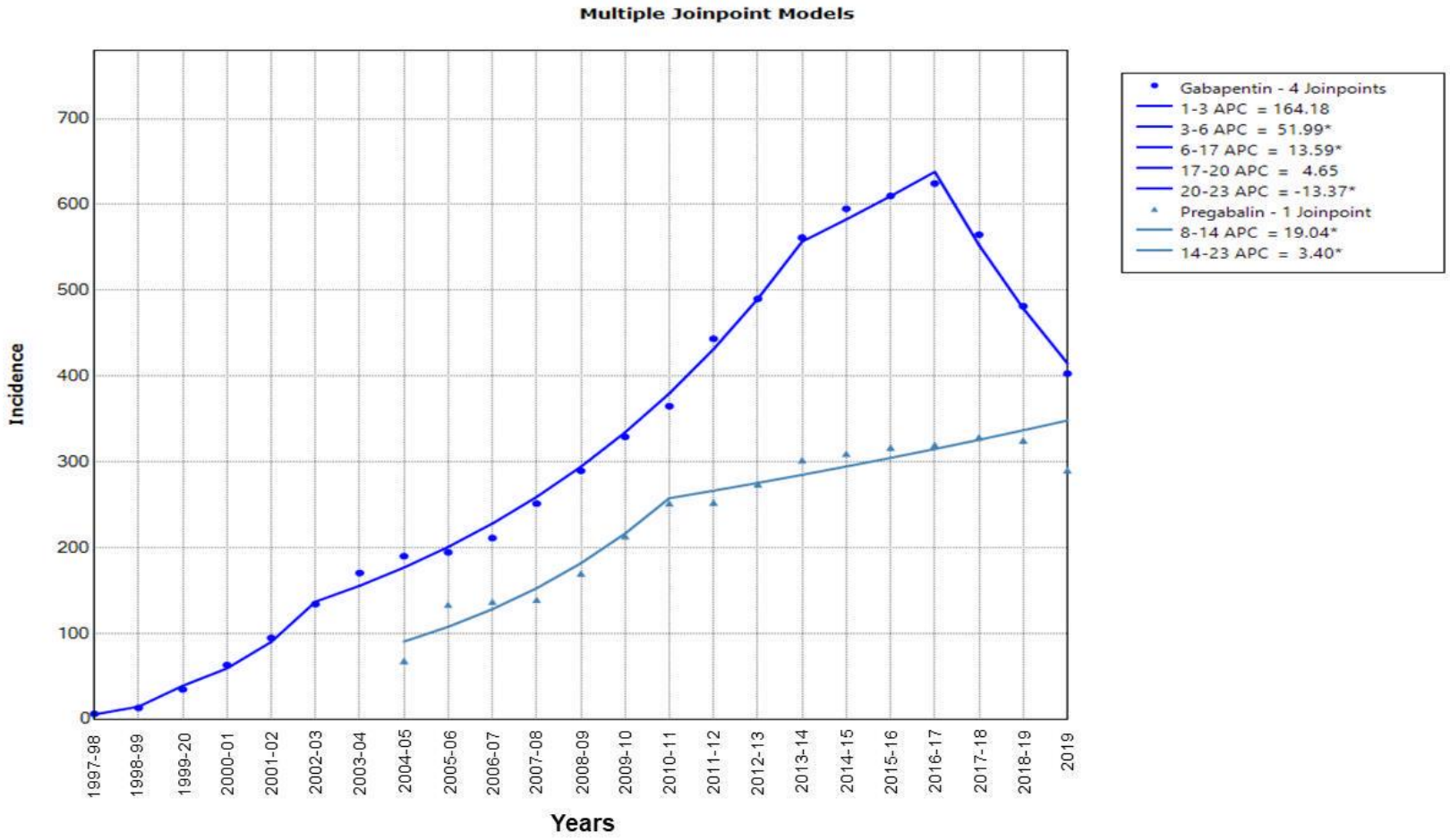
Characteristics	Gabapentin			Pregabalin		
	Incidence rate	95% CI		Incidence rate	95% CI	
		LCL	UCL		LCL	UCL
Overall	332.68	331.94	333.42	239.60	238.88	240.33
By age group						
18-24	57.06	56.13	58.01	49.91	48.92	50.93
25-34	130.77	129.68	131.87	108.48	107.31	109.65
35-44	249.71	248.23	251.20	196.03	194.50	197.58
45-54	389.69	387.77	391.62	282.90	281.02	284.79
55-64	473.47	471.13	475.82	320.38	318.18	322.60
65-75	572.77	569.83	575.72	377.83	375.10	380.59
75+	587.63	584.56	590.71	409.63	406.68	412.60
By sex						
Male	259.18	258.26	260.11	181.38	180.48	182.28
Female	404.96	403.81	406.11	296.94	295.81	298.08

Supplementary Table 4. Licensed and unlicensed indications resulting from meta-analysis of CPRD GOLD and AURUM data.

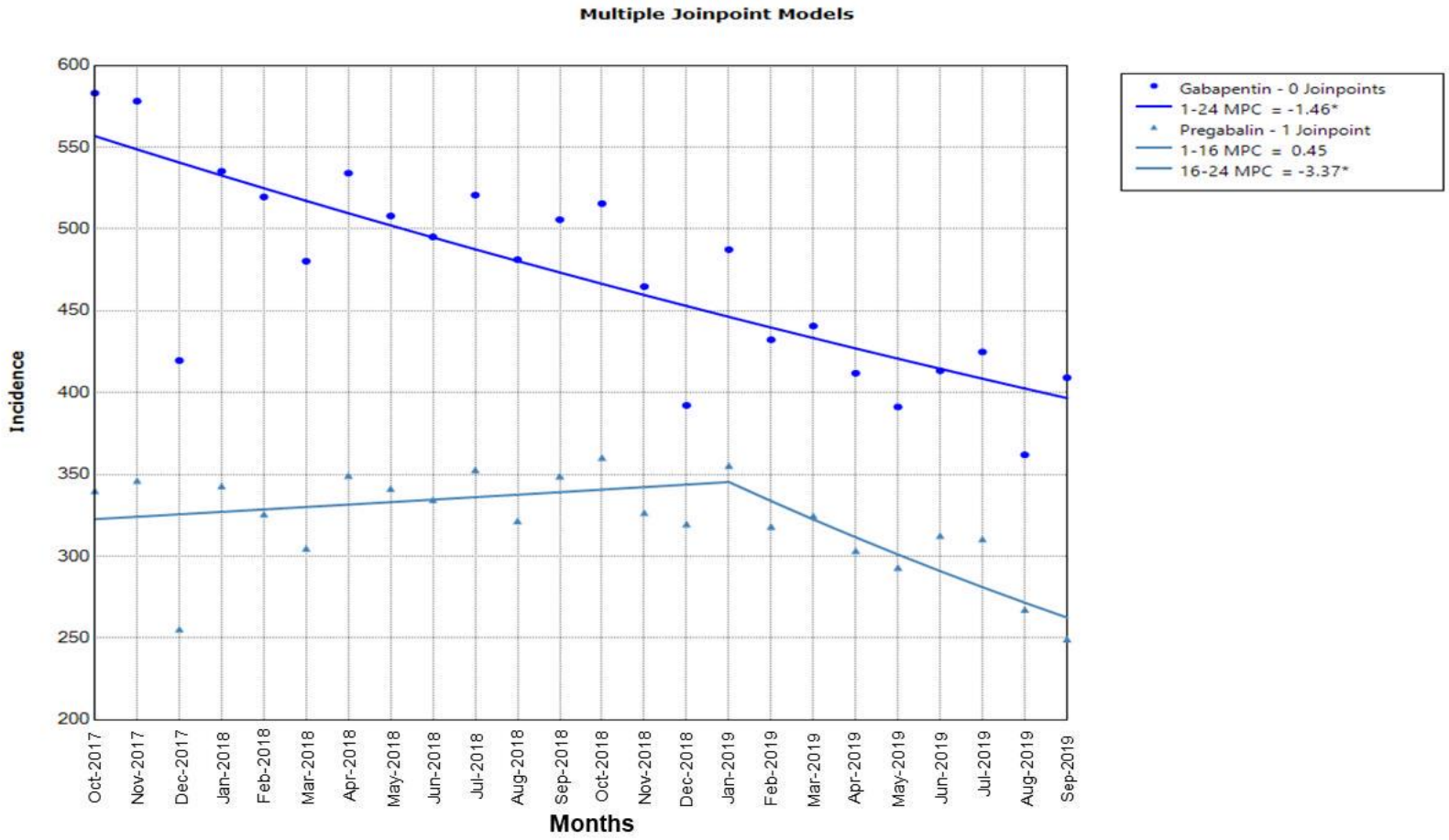
Indication	Gabapentin		Pregabalin	
Licensed	**Percentage of cohort (95% CI) with indication recorded ever before end of final treatment period**		**Percentage of cohort (95% CI) with indication recorded ever before end of final treatment period**	
Epilepsy	2·3 (2·3, 2·4)		2·9 (2·9, 3·0)	
Neuropathic pain	34·6 (34·5, 34·7)		33·9 (33·8, 34·1)	
Anxiety	10·1 (10·0, 10·2)†		14·6 (14·5, 14·7)	
Unlicensed	**Percentage of cohort (95% CI) with indication recorded (14 days before to 90 days after incident prescription)**	**Percentage of cohort (95% CI) with indication recorded (30 days before to 90 days after incident prescription)**	**Percentage of cohort (95% CI) with indication recorded (14 days before to 90 days after incident prescription)**	**Percentage of cohort (95% CI) with indication recorded (30 days before to 90 days after incident prescription)**
Chronic abdominal pain	0·3 (0·3, 0·3)	0·4 (0·3, 0·4)	0·4 (0·4, 0·4)	0·5 (0·4, 0·5)
Chronic back pain	14·6 (14·6, 14·7)	15·8 (15·7, 15·9)	12·6 (12·5, 12·7)	13·7 (13·6, 13·8)
Chronic headache	0·03 (0·02, 0·03)	0·03 (0·03, 0·04)	0·02 (0·02, 0·03)	0·03 (0·02, 0·03)
Chronic neck pain	0·8 (0·8, 0·8)	0·9 (0·9, 0·9)	0·7 (0·7, 0·7)	0·8 (0·7, 0·8)
Fibromyalgia	1·3 (1·3, 1·3)	1·4 (1·3, 1·4)	2·0 (2·0, 2·1)	2·2 (2·1, 2·2)
Migraine	0·2 (0·2, 0·2)	0·2 (0·2, 0·2)	0·2 (0·1, 0·2)	0·2 (0·2, 0·2)
Osteoarthritis	1·3 (1·3, 1·4)	1·5 (1·4, 1·5)	1·1 (1·0, 1·1)	1·2 (1·1, 1·2)
Restless legs	0·6 (0·6, 0·7)	0·7 (0·7, 0·7)	0·5 (0·4, 0·5)	0·5 (0·5, 0·5)

†Anxiety is not a licensed indication for gabapentin, only licensed for pregabalin

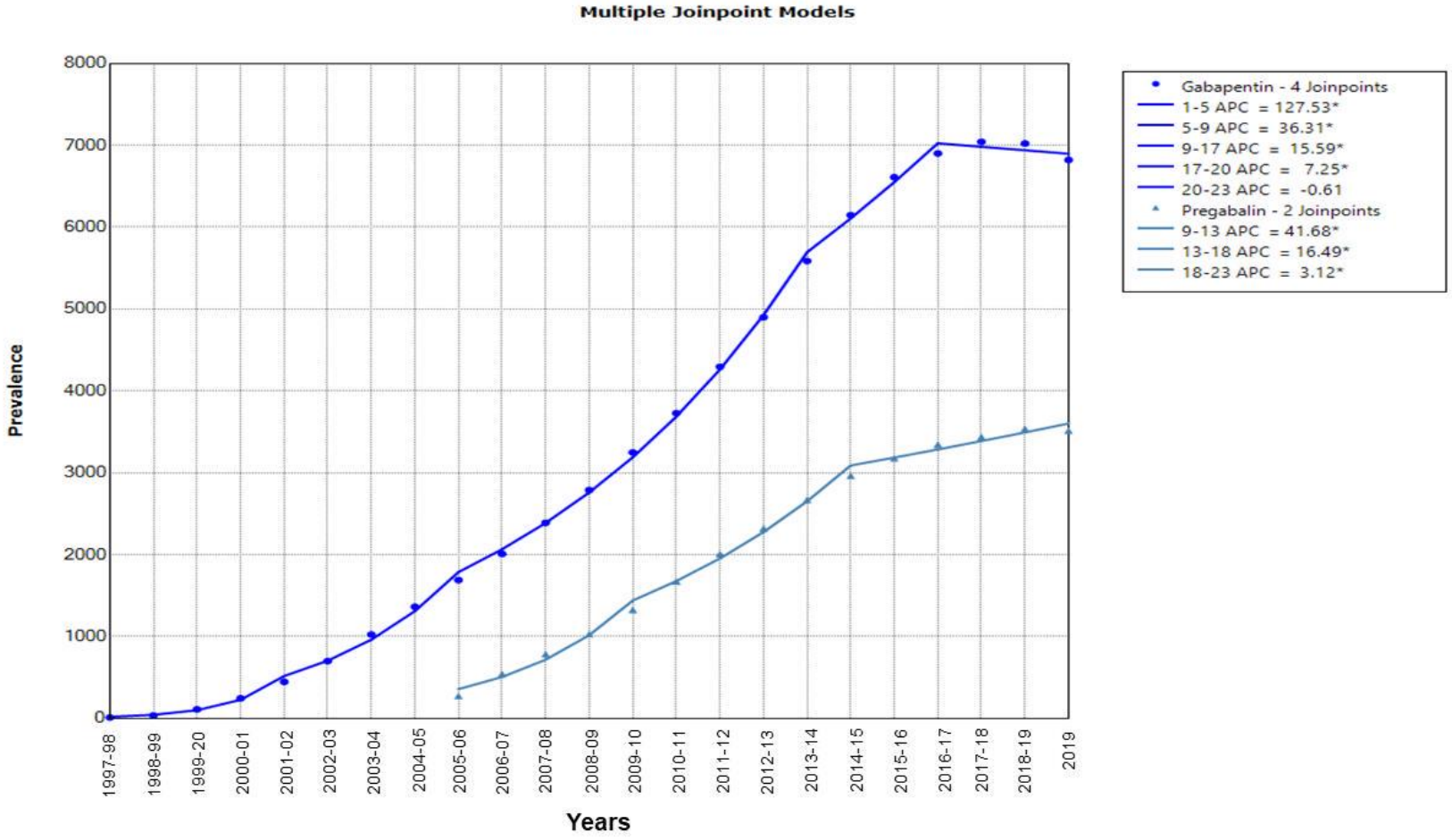
Supplementary Figure 1: Joinpoint Analysis Annual trend in incident gabapentinoid prescribing per 100,000 patient years (1997-2019)



Supplementary Figure 2: Joinpoint Analysis Monthly trend in incident gabapentinoid prescribing per 100,000 patient years (Oct-2017 to Sep-2019)



Supplementary Figure 3: Joinpoint Analysis Annual trend in prevalent gabapentinoid prescribing 100,000 patient years (1997-2019)



Supplementary Figure 4: Joinpoint Analysis Monthly trend in prevalent gabapentinoid prescribing 100,000 patient years (Oct-2017 to Sep-2019)