Online Resources

Title:

Identifying Maternal Conditions leading to Gabapentinoid Prescriptions in Pregnancy Using Electronic Health Records from Six European Countries - A contribution from the IMI ConcePTION project

Journal: Drug safety

Corresponding author: Anna-Belle Beau

Toulouse University Hospital, CERPOP-SPHERE Team, Inserm UMR 1295

37 allées Jules Guesde Bat C floor 3, 31000 Toulouse, France

anna-belle.beau@univ-tlse3.fr

Methods

eTable 1. Description of participating data sources

eTable 2. Detailed definitions of maternal conditions

eTable 3. Code lists used in the sensitivity analyses exploring variations in the identification of neuropathic pain.

Results

eTable 4. Proportions of maternal conditions leading to gabapentinoid dispensed from 3 months before start of pregnancy to the end of pregnancy in Finland, in the additional analyses as compared to the main analysis. n (%).

eTable 5. Proportions of maternal conditions leading to gabapentinoid dispensed from 2.5 months before start of pregnancy to the end of pregnancy in France, in the additional analyses as compared to the main analysis. n (%).

eTable 6. Proportions of maternal conditions leading to gabapentinoid dispensed from 1 year before start of pregnancy to the end of pregnancy in Italy, in the additional analyses as compared to the main analysis. n (%).

eTable 7. Proportions of maternal conditions leading to gabapentinoid dispensed from 1 year before start of pregnancy to the end of pregnancy in Norway, in the additional analyses as compared to the main analysis. n (%).

eTable 8 Proportions of maternal conditions leading to gabapentinoid dispensed from 1 year before start of pregnancy to the end of pregnancy in Spain, in the additional analyses as compared to the main analysis. n (%).

eTable 9. Proportions of maternal conditions leading to gabapentinoid prescribed from 1 year before start of pregnancy to the end of pregnancy in Wales, in the additional analyses as compared to the main analysis. n (%).

eFigure1. Proportions of maternal conditions leading to gabapentinoid prescribed/dispensed from 1 year before start of pregnancy to the end of pregnancy in the six data sources, varying the

window of assessment of the data components around gabapentinoid prescription/dispensing dates.

Country / Coverage	Name or registers	Description
Coverage Finland / National	Linkage of national registries: Medical birth registry, Prescription drug registry, National patient registry, Register of Primary Health Care visits	Medical birth registry: Information on births, pregnancy length, maternal parity, smoking, maternal age, maternal comorbidity, and pregnancy and birth complications. Prescription drug registry: Data on all prescription entitled to reimbursement fills from pharmacies including Anatomical therapeutical chemical (ATC) classification codes and dispensing date. Over the counter medicines and medicines used during in-patient hospital stays are not included. Data are available from three months before to three months after pregnancy. National patient registry: Health administrative registry from private and public specialist care. Data on inpatient stays and outpatient care contacts included diagnoses coded according to International Statistical Classification of Diseases and Related Health Problems revision 10 (ICD-10). Register of Primary Health Care visits: Health administrative registry from private service providers. Data on primary care visits contacts included diagnoses coded according to International Statistical Classification of Diseases and Related Health Problems revision 10 (ICD-10) or International Classification of
France / Haute- Garonne region	EFEMERIS database	 Primary Care, second edition (ICPC-2). EFEMERIS database includes data on pregnant women covered by the French Health Insurance System in Haute-Garonne (south-west France). Specifically, EFEMERIS comprises data about (a) all prescriptions redeemed at pharmacies by women in ambulatory care, prior to and during pregnancy [names, Anatomical, Therapeutic and Chemical classification system (ATC) and dispensing dates] (b) the mother (age, level of education) and the child (gender, birth size, birth weight, congenital anomalies) through children's certificates filled out during the compulsory medical examinations at birth, 9 and 24 months, (c) Terminations Of Pregnancy for Fetal Anomaly (TOPFAs) that has been considered in the maternities of the region, (d) nature and date of termination of pregnancy (elective termination, stillbirth, and spontaneous abortion) from the Toulouse University Hospital centre, and (e) data on inpatient stays during pregnancy included diagnoses coded according to International Statistical Classification of

eTable 1. Description of participating data sources

		Diseases and Related Health Problems revision
		10 (ICD-10).
Italy / Emilia Romagna region	Linkage of Emilia-Romagna administrative databases and registries. Inhabitant registry, drug dispensations from community pharmacies and from hospital pharmacies, hospital discharge records, emergency admissions, outpatient services, exemptions from copayment, mental health services, birth registry, and death registry	Emilia-Romagna registries include birth, death, and anagraphic registries. Birth registry collect information on births, type of pregnancy, date of delivery, type of pregnancy outcome, pregnancy length, weight at birth, maternal age. Administrative databases collect information about drug dispensation from community and hospital pharmacy including ATC code and dispensing quantity and date. Hospital discharge record collect data about inpatients stay, including diagnosis (ICD9) as well as emergency admission database and mental health services databases collect data from outpatients. Moreover, exemptions from copayment databases collect information about
		exemption related to specific diagnostic code.
Norway / National	Linkage of national registries: Medical birth registry, Prescription drug registry, National patient registry, Register of Primary Health Care visits	Medical birth registry: Includes information on all births in Norway since 1967, including information on pregnancy length, maternal parity, smoking, maternal age, maternal health, pregnancy, delivery, and neonatal outcomes. Prescription drug registry: Includes data on all dispensed prescription from pharmacies in Norway to outpatients since 2004 including Anatomical therapeutical chemical (ATC) classification codes, amount dispensed (DDD) and dispensing date. National patient registry: Health administrative registries from private and public specialist care in all of Norway from 2008. Data on inpatient hospital stays and outpatient specialist care contacts included diagnoses coded according to ICD-10. Norwegian Control and Payment of Health Reimbursements database (KUHR): The KUHR Database is an administrative database based on reimbursement claims from physicians. It contains information from primary health care/GP/emergency services on morbidity, utilization of health care services and health care use from 2006. Diagnostic codes in the KUHR follow ICD-10, but also ICPC with is more frequently used by GPs. For more information, see
Spain / Valencian region	Linkage of administrative databases and registries: Perinatal Mortality Registry (RMPCV); Birth Registry (META-B); Congenital Anomaly Population-based Registry (RPAC-CV); Prescription and dispensations	https://helsedata.no/en Birth Registry (for live births), Perinatal Mortality Registry (for stillbirths and live births deaths during the first 28 days of life) and Congenital Anomaly Population-based Registry (for stillbirths and live births with at least 1 major congenital anomaly): Information on births, type of pregnancy, date of delivery,

	dataset (GAIA); Morbidity- Hospital discharges database (CMBD)	 type of pregnancy outcome, pregnancy length, weight at birth, maternal age. Prescription and dispensations dataset: Data on all prescription and dispensation to outpatients entitled to reimbursement fills from pharmacies including Anatomical therapeutic chemical (ATC) classification codes and dispensing date. Morbidity- Hospital discharges database: Health administrative registries from private and public inpatients care. Data on inpatient stays included diagnoses coded according to International Classification of Diseases: ICD 9th version until 2015 and10th revision Spanish Version (ICD-10ES) 2016 onwards.
UK / Wales country: 85% of primary care practices	SAIL databank, including in- patient and primary care records, emergency care, ONS births and deaths, and data (including all prescriptions and vaccinations) from ~80% of Wales GP practices	National, whole-population data, with the exception of primary care practices. Practices contribute voluntarily, without additional funding. For details see Ford et al 2009, Lyons et al 2009.

eTable 2. Detailed definitions of maternal conditions

Condition	Finland Derivation	France Derivation	Italy Derivation	Norway Derivation	Spain Derivation	Wales Derivation
Epilepsy	One of the following: - Specific reimbursement entitlement codes for epilepsy: 111, 181, 182, 183,199,	Oneofthefollowing: ICD-10 codes forepilepsy:G40, G41,OR;-DispensingofASMs:N03 (except)	One of the following: - ICD-9 codes for epilepsy: 345.xx, 780.3x, 17, RF0060, OR; - ICD-10 codes for	One of the following: - ICPC-2 codes for epilepsy: N88, N07, OR; - ICD-10 codes for epilepsy: G40, G41,	One of the following: - ICD-9 codes for epilepsy: 345.xx, 780.3x, OR; - ICD-10ES codes for epilepsy: R56.9,	One of the following: - ICD-10 code for epilepsy : G40 (Epilepsy), G41 (Status epilepticus), OR;
	OR; - ICPC-2 codes for epilepsy: N88, N07, OR; - ICD-10 codes for epilepsy: G40, G41, OR; - Dispensing of ASMs: N03	N03AF01)	epilepsy: G40, G41, OR; - Dispensing of ASMs: N03 (except N03AF01- carbamazepine)	OR; - Dispensing of ASMs : N03	R56.1, F44.5, OR; - Dispensing of ASMs : N03 (except N03AF01- carbamazepine)	 - READv2 code for epilepsy: F25 (Epilepsy), 1O30. (Epilepsy confirmed), 667B. (Nocturnal epilepsy), OR; - Prescribing of ASMs: N03 (except N03AF01- carbamazepine)
Neuropathic pain	One of the following: - Specific prescriber specialty of the gabapentinoid prescription: Rheumatologist (value=570, 742), Anesthesiologist (value=100), Orthopedist	One of the following: - Specific prescriber specialty of the gabapentinoid prescription: Rheumatologist (value=14), Anesthesiologist (value=2), Orthopedist (value=41), OR;	One of the following: - ICD-9 codes for pain: diabetic neuropathy (250.6, 357.2), postherpetic neuralgia (053.1), back pain with neuropathic involvement (722.1, 722.2, 722.7, 724.0, 724.3, 724.4), neck pain with	One of the following: - Specific prescriber specialty of the gabapentinoid prescription: Rheumatologist (value=41), Anesthesiologist (value=2), Orthopedic surgeon (value=84, 152), OR;	One of the following: - ICD-9 codes for pain : diabetic neuropathy (250.6, 357.2), postherpetic neuralgia (053.1), back pain with neuropathic involvement (722.1, 722.2, 722.7, 724.0, 724.3, 724.4), neck pain with	Oneofthefollowing:ICD-10 code forpain:R52, OR;-READv2 code forneuropathic pain:N2423 (Neuropathicpain), OR;Pain specific co-prescribing:N01BX04-capsaicin,

- ICPC-2 codes for pain: A01, L86 OR; m N	pain: R52, OR;	722.0, 723.0, 723.4),	pain: A01, L86 OR;		1 .
pain: A01, L86 OR; m			pani. A01, Lou OK,	722.0, 723.0, 723.4),	plaster
- ICD-10 code for N pain: R52, OR; N	- Pain specific co- medications: N02A, N01BX04, N01BB02, N02BG08, M03AX01	cancer (140.0–172.9, 174.0–208.9), with neuropathic involvement (337.2, 353.2, 353.3, 353.4, 354.4, 355.7, 355.9, 729.2, 353.0, 353.1, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.6, 355.8, 357.3, 357.8, 357.9), causalgia, reflex sympathetic dystrophy, and related disorders (337.2, 353.2, 353.3, 353.4, 354.4, 355.7, 355.9, 729.2), HIV/AIDS (042.0) with neuropathic involvement (337.2, 353.2, 353.3, 353.4, 354.4, 355.7, 355.9, 729.2, 353.0, 353.1, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3,	 ICD-10 code for pain: R52, G50- G59; G60-G64; G95.85; E10.4; E11.4; OR; Pain specific co- medications: N02AX02, N01BX04, N01BB02, N02A, M03AX01 	722.0, 723.0, 723.4), cancer (140.0–172.9, 174.0–208.9), with neuropathic involvement (337.2, 353.2, 353.3, 353.4, 354.4, 355.7, 355.9, 729.2, 353.0, 353.1, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3, 354.5, 354.8, 354.9, 355.0, 355.1, 355.2, 355.6, 355.8, 357.3, 357.8, 357.9), causalgia, reflex sympathetic dystrophy, and related disorders (337.2, 353.2, 353.3, 353.4, 354.4, 355.7, 355.9, 729.2), HIV/AIDS (042.0) with neuropathic involvement (337.2, 353.2, 353.3, 353.4, 354.4, 355.7, 355.9, 729.2, 353.0, 353.1, 353.8, 353.9, 354.0, 354.1, 354.2, 354.3,	plaster

355.3, 3	355.4, 355.5,	355.3, 355.4, 355.5,
355.6, 3	355.8, 357.4,	355.6, 355.8, 357.4,
357.8, 3	57.9),	357.8, 357.9),
phanton	n limb pain	phantom limb pain
(353.6),	trigeminal	(353.6), trigeminal
neuralg	ia (350.1),	neuralgia (350.1),
atypical	facial pain	atypical facial pain
(350.2,	352.1), other	(350.2, 352.1), other
disorder	rs of	disorders of
periphe	ral nervous	peripheral nervous
system	associated	system associated
with net	uropathic	with neuropathic
pain (35	53.0, 353.1,	pain (353.0, 353.1,
353.8, 3	353.9, 354.0,	353.8, 353.9, 354.0,
354.1, 3	354.2, 354.3,	354.1, 354.2, 354.3,
354.5, 3	354.8, 354.9,	354.5, 354.8, 354.9,
355.0, 3	355.1, 355.2,	355.0, 355.1, 355.2,
355.3, 3	355.4, 355.5,	355.3, 355.4, 355.5,
355.6, 3	355.8)	355.6, 355.8)
- ICD-1	0 code for	- ICD-10ES code
pain: R	52 , OR;	for pain: R52, OR;
- Pain s	pecific co-	- Pain specific co-
medica	-	medications: N02A-
	02-tramadol,	strong opioids,
	04-capsaicin,	N01BX04-capsaicin,
	02-lidocaine	N01BB02-lidocaine
	N02AA01-	plaster, N02BG08-
morphin		ziconotide,
N02AA		M03AX01-
oxycode	one,	botulinum toxin A
N02AX	06-	
	1	

		tapentadol, N02BG08- ziconotide, N07BC02- methadone, M03AX01- botulinum toxin A			
Generalised anxiety disorder - ICPC-2 codes for anxiety: P01, P02, P74, OR; - ICD-10 codes for anxiety: F40, F41, F42, F43, OR; - Anxiety specific co- medications: N06A (except N06AA or N06AX)	 e One of the following: - Specific prescriber specialty of the gabapentinoid prescription: psychiatrist (value=33, 75), OR; - ICD-10 codes for anxiety: F40, F41, F42, F43, OR; - Anxiety specific co-medications: N05BA, N06A (except N06AA or N06AX21) 	One of the following: - ICD-9 codes for anxiety: 300.0 (anxiety states), 300.00 (anxiety states, unspecified), 300.02 (generalized anxiety disorders), 300.09 (other anxiety states), 309.21 (separation anxiety disorder), OR; - ICD-10 codes for anxiety: F40, F41, F42, F43, OR; - Anxiety specific co- medications: N05BA- benzodiazepine derivatives, N06A- antidepressants (except tricyclic antidepressive agents (N06AA) and SNRI (N06AX))	One of the following: - Specific prescriber specialty of the gabapentinoid prescription: psychiatrist (value=58), OR; - ICPC-2 codes for anxiety: P01, P02, P74, OR; - ICD-10 codes for anxiety: F40, F41, F42, F43, OR; - Anxiety specific co- medications: N05BA, N06A (except N06AA or N06AX)	One of the following: - ICD-9 codes for anxiety: 300.0 (anxiety states), 300.00 (anxiety states, unspecified), 300.02 (generalized anxiety disorders), 300.09 (other anxiety states), 309.21 (separation anxiety disorder), OR; - ICD-10ES codes for anxiety: F40, F41, F42, F43, OR; - Anxiety specific co-medications: N05BA- benzodiazepine derivatives, N06A- antidepressants (except tricyclic antidepressive agents (N06AA) and	One of the following: - ICD-9 codes for anxiety: 300.0 (anxiety states), 300.00 (anxiety states, unspecified), 300.02 (generalized anxiety disorders), 300.09 (other anxiety states), 309.21 (separation anxiety disorder), OR; - ICD-10 codes for anxiety: F40, F41, F42, F43, OR; - READ code for anxiety: E20, Eu40. (anxiety disorders), Eu41. (others anxiety disorders), Eu34114 (Persistant anxiety depression), OR; - READv2 code for anxiety: E20,

		duloxetine (N06AX21))	Eu40., Eu41., Eu34114 - Anxiety specific co-medications: N05BA- benzodiazepine
			derivatives, N06A-
			antidepressants
			(except tricyclic
			antidepressive agents
			(N06AA) and
			duloxetine
			(N06AX21))

Footnote: ASM: antiseizure medication

Paper used	Coding	Specific codes			
	system				
Viniol A et	ICD-10 codes	B02 herpes zoster			
al. BMJ		G500 trigeminal neuralgia			
Open 2019		G530 post zoster neuralgia			
1		G546 phantom pain			
		G9585 deafferentation pain due to spinal cord impairment			
		M797 fibromyalgia			
		T926 stump pain after traumatically arm amputation			
		T936 stump pain after traumatically leg amputation			
		G130 paraneoplastic neuromyopathy and neuropathy			
		G521 diseases of N. glossopharyngeus and glossopharyngeus			
		neuralgia			
		G56 mono neuropathy of the upper extremity			
		G57 mono neuropathy of the lower extremity			
		G58 other mono neuropathies			
		G59 mono neuropathy parallel to other illness			
		G60 hereditary and idiopathic neuropathy			
		G61 polyneuritis			
		G62 other polyneuropathies			
		G63 polyneuropathy parallel to other illness			
		G990 autonomous neuropathy through endokrinal and metabolic			
		diseases			
		M501 cervical intervertebral disc degeneration with radiculopathy			
		M511 lumbal intervertebral disc degeneration with radiculopathy			
		M541 radiculopathy			
		M542 cervical neuralgia			
		M543 ischialgia			
		M544 lumboischialgia			
Wettermark	ICD-10 codes	Unspecified pain (M79, R52) and further 40 diagnoses			
B et al.		related to central or peripheral neuropathic			
International		pain (ICD-10 codes G35.9, G50.0, G50.1, G51.0,			
Journal of		G53.0, G54.4, G54.6, G55.0, G55.1, G56.0, G56.2,			
Clinical		G56.4, G56.9, G57.0, G57.1, G57.8, G57.9, G58.0,			
Practice		G58.7, G58.8, G62.9, G63.2, G82.1, G95.0, G95.2,			
2014		G95.8, G97.9, I69.1, I69.3, M48.0, M50.1, M53.0,			
		M53.1, M54.1, M54.3, M54.4, M79.2 and M89.0).			

eTable 3. Code lists used in the sensitivity analyses exploring variations in the identification of neuropathic pain.

eTable 4. Proportions of maternal conditions leading to gabapentinoid dispensed from 3 months before start of pregnancy to the end of pregnancy in Finland, in the additional analyses as compared to the main analysis. n (%).

		Main analysis ± 1 year from each	Varying identification of neuropathic pain		
Medication	Maternal condition	gabapentinoid prescription /dispensing dates	Using codes from eTable 3 (Viniol A et al. 2019)	Using codes from eTable 4 (Wettermark B et al. 2014)	
Any	Any condition ^a	1534 (63.8)	1809 (75.2)	1835 (76.3)	
gabapentinoids	Epilepsy ^b	360 (15.0)	360 (15.0)	360 (15.0)	
(N=2406)	Anxiety ^b	1011 (42.0)	1011 (42.0)	1011 (42.0)	
	Neuropathic pain ^b	759 (31.5)	1231 (51.2)	1262 (52.5)	

eTable 5. Proportions of maternal conditions leading to gabapentinoid dispensed from 2.5 months before start of pregnancy to the end of pregnancy in France, in the additional analyses as compared to the main analysis. n (%).

		Main analysis ± 1 year from each	Varying identification of neuropathic pain		
Medication	Maternal condition	gabapentinoid prescription /dispensing dates	Using codes from eTable 3 (Viniol A et al. 2019)	Using codes from eTable 4 (Wettermark B et al. 2014)	
Any	Any condition ^a	163 (60.6)	171 (63.6)	164 (61.0)	
gabapentinoids	Epilepsy ^b	17 (6.3)	17 (6.3)	17 (6.3)	
(N=269)	Anxiety ^b	62 (23.0)	62 (23.0)	62 (23.0)	
	Neuropathic pain ^b	134 (49.8)	145 (53.9)	135 (50.2)	

eTable 6. Proportions of maternal conditions leading to gabapentinoid dispensed from 1 year before start of pregnancy to the end of pregnancy in Italy, in the additional analyses as compared with the main analysis. n (%).

		Main analysis ± 1 year from	Varying identification of neuropathic pain		
Medication	Maternal condition	each gabapentinoid prescription /dispensing dates	Using codes from eTable 3 (Viniol A et al. 2019)	Using codes from eTable 4 (Wettermark B et al. 2014)	
Any	Any condition ^a	396 (43.6)	398 (43.8)	396 (43.6)	
gabapentinoids	Epilepsy ^b	122 (13.4)	122 (13.4)	122 (13.4)	
	Anxiety ^b	238 (26.2)	238 (26.2)	238 (26.2)	
(N=908)	Neuropathic pain ^b	165 (18.2)	167 (18.4)	165 (18.2)	

eTable 7. Proportions of maternal conditions leading to gabapentinoid dispensed from 1 year before start of pregnancy to the end of pregnancy in Norway, in the additional analyses as compared with the main analysis. n (%).

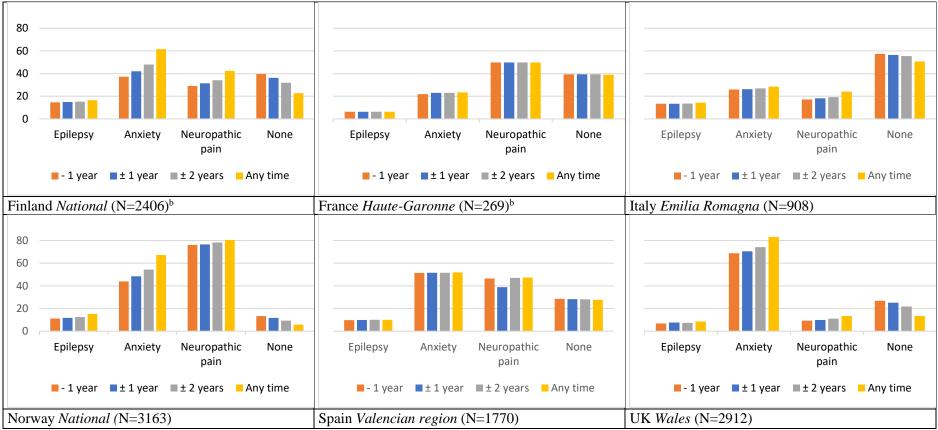
	Maternal condition	Main analysis ± 1 year from each	Varying identification of neuropathic pain	
Medication		gabapentinoid prescription /dispensing dates	Using codes from eTable 3 (Viniol A et	Using codes from eTable 4 (Wettermark B
		/uispensing uates	(Vinior A et al. 2019)	et al. 2014)
Any gabapentinoids (N=3163)	Any condition ^a	2797 (88.4)	2816 (89.0)	2843 (89.9)
	Epilepsy ^b	372 (11.8)	372 (11.8)	372 (11.8)
	Anxiety ^b	1538 (48.6)	1538 (48.6)	1538 (48.6)
	Neuropathic pain ^b	2431 (76.9)	2461 (77.8)	2504 (79.2)

eTable 8. Proportions of maternal conditions leading to gabapentinoid dispensed from 1 year before start of pregnancy to the end of pregnancy in Spain, in the additional analyses as compared with the main analysis. n (%).

	Maternal condition	Main analysis ± 1 year from each gabapentinoid prescription /dispensing dates	Varying identification of neuropathic pain	
Medication			Using codes from eTable 3 (Viniol A et al. 2019)	Using codes from eTable 4 (Wettermark B et al. 2014)
Any gabapentinoids (N=1770)	Any condition ^a	1269 (71.7)	1291 (72.9)	1270 (71.8)
	Epilepsy ^b	176 (9.9)	176 (9.9)	176 (9.9)
	Anxiety ^b	911 (51.5)	911 (51.5)	911 (51.5)
	Neuropathic pain ^b	827 (46.7)	864 (48.8)	835 (47.2)

eTable 9. Proportions of maternal conditions leading to gabapentinoid prescribed from 1 year before start of pregnancy to the end of pregnancy in Wales, in the additional analyses as compared with the main analysis. n (%).

	Maternal condition	Main analysis ± 1 year from each gabapentinoid prescription /dispensing dates	Varying identification of neuropathic pain	
Medication			Using codes from eTable 3 (Viniol A et al. 2019)	Using codes from eTable 4 (Wettermark B et al. 2014)
Any	Any condition ^a	2180 (74.9)	2312 (79.4)	2269 (77.9)
gabapentinoids (N=2912)	Epilepsy ^b	206 (7.1)	206 (7.1)	206 (7.1)
	Anxiety ^b	2054 (70.5)	2054 (70.5)	2054 (70.5)
	Neuropathic pain ^b	288 (9.9)	885 (30.4)	773 (26.6)



eFigure1. Percentage of maternal conditions leading to gabapentinoid prescribed/dispensed from one year before start of pregnancy to the end of pregnancy in the six data sources^a, varying the window of assessment of the data components around gabapentinoid prescription/dispensing dates.

Footnote: ^aIn the Finnish and French data source, gabapentinoid prescription/dispensing was assessed from 3 months and 2.5 months before pregnancy start until end of pregnancy, respectively,