

Supplementary materials

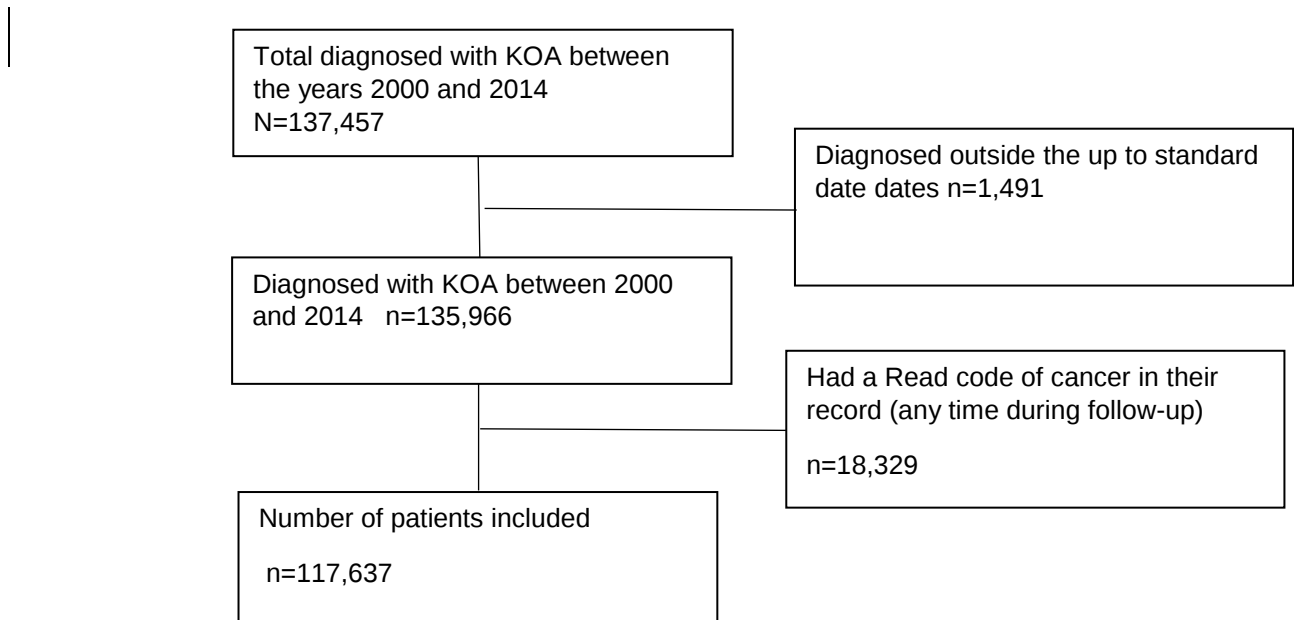


Figure S1 selection of study population

Table S1 study drug classes, individual drugs and corresponding DDD values

	Drug Class and Subclasses	Specific Drugs	DDD (mg)	Individual Drugs	DDD (mg)
1.	Antidepressants				
	Tricyclic antidepressants (TCA)	Amitriptyline	75	Nortriptyline	75
		Imipramine	100	Doxepin	100
		Clomipramine	100	Dosulepin	150
		Lofepramine	105	Amoxapine	150
	Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	20	Escitalopram	10
		Paroxetine	20	Sertraline	50
		Citalopram	20	Fluvoxamine	100
	Monoamine oxidase inhibitors (MAOIs)	Isocarboxazide	15	Meclobemide	300
		Phenelzine	60	Tranylcypromine	10
	Other antidepressants	Agomelatine	25	Mirtazapine	30
		Trazodone	300	Reboxetine	8
		Nefazodone	400	Mianserine	60
		Venlafaxine	100	Duloxetine	60
2.	AEDs				
	Older	Phenobarbital	100	Valproic acid	1500
		Ethosuximide	1250	Carbamazepine	1000
		Phenytoin	300	Clonazepam	8
		Primidone	1250		
	Newer	Levetiracetam	1500	Vigabatrin	2000
		Tiagabine	30	Pregabalin	300
		Lamotrigine	300	Lacosamide	300
		Gabapentin	1800	Rufinamide	1400
		Felbamate	2400	Zonisamide	200
		Oxcarbazepine	1000	Retigabine	900

Table S1 study drug classes, individual drugs and corresponding DDD values, *continued*

	Drug Class and Subclasses	Specific Drugs	DDD (mg)	Individual Drugs	DDD (mg)
3.	NSAIDs				
	Selective COX-2				
	Coxibs	Celecoxib	200	Etoricoxib	60
		Rofecoxib	25		
	Moderate COX-2 selective	Etodolac	400	Nemisulide	??
	Oxicams	Meloxicam	15	Piroxicam	20
		Tenoxicam	20		
	Drugs with COX-1 & COX-2 activity				
		Diclofenac	100	Indomethacin	100
		Ibuprofen	1200	Nabumetone	1000
		Ketoprofen	150	Aceclofenac	200
		Dexibuprofen	800	Mefenamic acid	1000
		Dexketoprofen	75	Phenylbutazone	300
		Fenbufen	600	Fenoprofen	1200
		Tiaprofenic acid	600	Flurbiprofen	200
		Acemetacine	120	Naproxen	500
		Tolmetin	700	Ketorolac	30
4.	Paracetamol		3000		
DDD: defined daily doses in mg; AEDs: anti-epileptic drugs; COX: cyclooxygenase inhibitor, NSAID non-steroidal anti-inflammatory drugs					

Table S2 List of Opioids, Corresponding DDD and Equianalgesic Ratios

Opioid Group	Drug	Route/Formulation	DDD	Equianalgesic Ratio
Stronge	Morphine	Oral	100	1
	Oxycodone	Oral	75	1.125
	Fentanyl	Transdermal	1.2	100
	Fentanyl	Transmucosal	0.6	50
	Tramadol	Oral	300	0.2
	Buprenorphine	Transdermal	1.2	100
	Buprenorphine	Sublingual	1.2	50
	Tapentadol	Oral	400	0.4
	Pethidine	Oral	400	0.1
	Hydromorphone	Oral	20	1.5
Weak	Codeine	Oral	120	0.1
	Dihydrocodeine	Oral	150	0.13
	Dextropropoxyphene	Oral	140	0.15
DDD: defined daily dose; Equianalgesic ratio: potency of respective opioid or opioid formulation compared with oral morphine. Source: Svendsen et al. (2012)				

Table S3 Characteristics of study population stratified according to analgesic

Analgesic Class	Antidepressants	AEDs	Opioids	NSAIDs	Paracetamol
No. patients	n=53,467	n=15,814	n=93,007	n=84,750	n=82,497
Gender (% of total prescribed respective class)					
Males	16,978 (31.7)	5,441 (34.4)	36,407 (39.1)	34,314 (40.5)	30,634 (37.2)
Female	36,489 (68.3)	10,373 (65.6)	56,600 (60.9)	50,436 (59.5)	51,863 (62.8)
Age at therapy initiation (years)					
Mean (SD)	64.46 (13.90)	66.95 (12.96)	64.69 (12.83)	62.58 (12.83)	66.98(12.40)
Age ranks (years) of all patients with KOA (% of total prescribed respective class)					
<40	2,150 (4.0)	337 (2.1)	2,906 (3.1)	3,492 (4.1)	1,813 (2.2)
40–64	25,127 (47.0)	6,420 (40.6)	43,478 (46.8)	44,688 (52.7)	32,842 (39.8)
65–80	18,278 (34.2)	6,409 (40.5)	35,447 (38.1)	28,982 (34.2)	35,421 (42.9)
>80	7,912 (14.8)	2,648 (16.8)	11,176 (2.0)	7,588 (9.0)	12,421 (15.6)
Males with KOA (% of total males prescribed respective drug class)					
<40	642 (3.8)	106 (1.9)	1,156 (3.2)	1,491 (4.4)	615 (2.0)
40–64	8,513 (50.1)	2,305 (42.4)	18,264 (50.2)	19,547 (56.9)	12,904 (42.1)
65–80	5,693 (33.5)	2,265 (41.6)	13,626 (37.4)	11,108 (32.4)	13,318 (43.5)
>80	2,130 (12.5)	765 (14.1)	3,361 (9.2)	2,168 (6.3)	3,797 (12.4)
Total (100%)	16,978	5,441	36,407	34,314	30,634
Females (% of total females prescribed respective drug class)					
<40	1,508 (4.1)	231 (2.2)	1,750 (3.1)	2001 (3.9)	1,198 (2.4)
40–64	16,614 (45.5)	4,115 (39.7)	25,214 (44.5)	25,141 (49.9)	19,938 (38.4)
65–80	12,585 (34.5)	4,144 (39.9)	21,821 (38.6)	17,874 (35.4)	22,103 (42.6)
>80	5,782 (15.9)	1,883 (18.2)	7,815 (13.8)	5,420 (10.8)	8,624 (16.6)
Total (100%)	36,489	10,373	56,600	50,436	51,863
AED: antiepileptic drugs; NSAID: Non-steroidal anti-inflammatory drugs; SD: standard deviation					

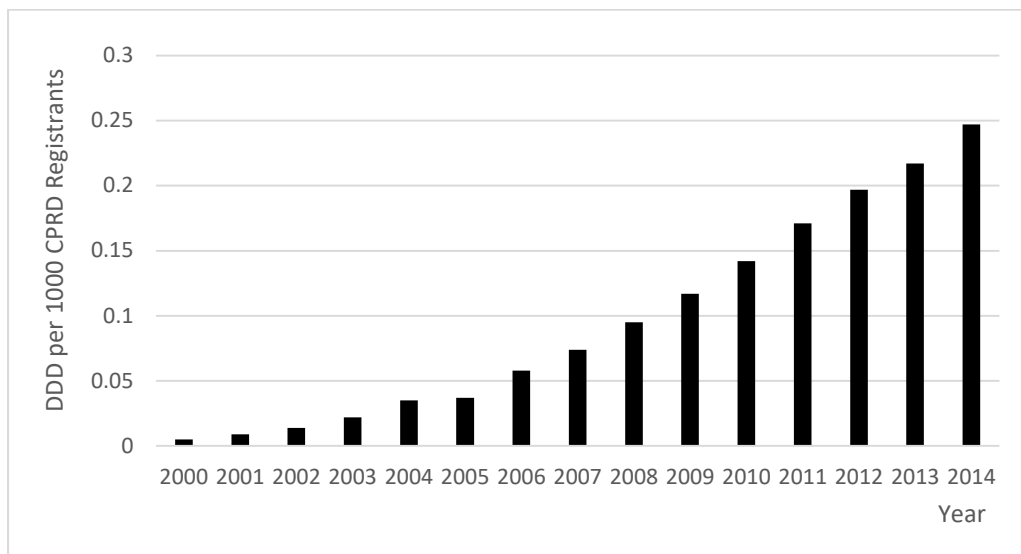


Figure S2 Mean Annual DDD per 1000 Registrants for Gabapentinoids

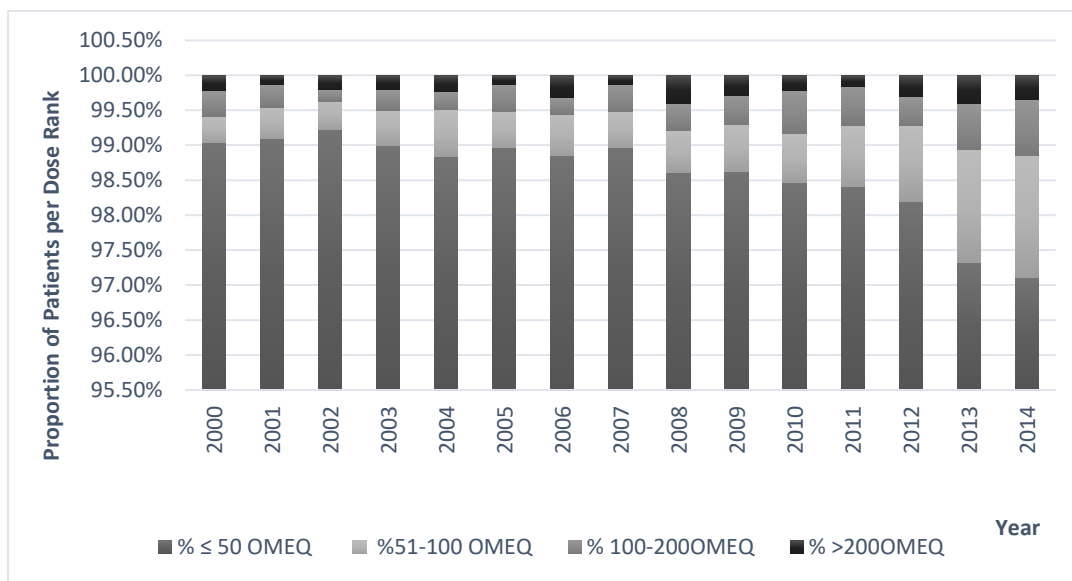


Figure S3 Proportion of Patients Prescribed Various OMEQ (mg/day) Dose Ranks

Table S4 Mean Number of Days' Supply in 2000 and 2014 for Study Drug Classes

	Mean annual days' supply		Percentage change between 2000 and 2014
	2000	2014	
Antidepressants	167.2 (SD 129.3)	186.9 (SD 143.7)	11.8
AEDs	91.1 (SD 100.1)	73.4 (SD 89.1)	19.4*
Opioids	66.9 (SD 92.6)	86.8 (SD 112.6)	29.7
NSAIDs	158.7 (SD 129.0)	184.4 (SD 144.3)	16.2
paracetamol	55.7 (SD 78.9)	71.9 (SD 91.6)	29.1

*Decrease