Use of Pregabalin – A Nationwide Pharmacoepidemiological Drug Utilization Study with Focus on Abuse Potential

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Key words
- pregabalin
- abuse
- drug utilization
- denmark

Abstract

Introduction: Pregabalin is currently approved for the treatment of epilepsy, generalized anxiety disorder and neuropathic pain with a licensed dosage range of 150 mg to 600 mg/day. Growing concern about the abuse potential of pregabalin is partly based on reports of pregabalin being used in dosages that exceed the approved therapeutic range.

Methods: To identify predictors of pregabalin use above recommended dosage, we conducted a pharmacoepidemological drug utilization study using the Danish nationwide registers. We deployed 4 measures of abuse: high use (≥ 600 mg/day) or very high use (≥ 1 200 mg/day) over a 6- or 12-month period, respectively. Multiple logistic regression was used to identify patient and treatment characteristics that were associated with either abuse marker.

Results: Out of 42 520 pregabalin users 4 090 (9.6 %) were treated with more than 600 mg/day for 6 months and 2 765 (6.5 %) for more than 12 months. Male gender and prescription of antipsychotics and benzodiazepines were associated with increased risk of use of above the recommended dosage.

Discussion: Use of pregabalin above recommended dosages was rare but abuse may occur in susceptible patients.

Introduction

In Europe, pregabalin is approved for the treatment of epilepsy, neuropathic pain and generalized anxiety disorder (GAD). In the US pregabalin is approved for fibromyalgia, postherpetic neuralgia and neuropathic pain following spinal cord injury or diabetes, but not for GAD [1]. Additionally, case reports and smaller studies have suggested an effect for hypnotic-dependent insomnia [2], withdrawal of benzodiazepines [3] and alcohol dependence [4].

The use of pregabalin has increased throughout the world and growing concerns about the abuse potential pregabalin have emerged [5–7]. Euphoria occurs as a frequent side effect of pregabalin [8] and several cases of overdose from recreational use have been reported [5,9,10]. Reports of tampering in which pregabalin was used by alternative routes of administration, i.e., nasal insufflation or venous injection, have also been reported [11,12].

Some patient groups may be particularly susceptible to pregabalin abuse. A study by Grosshans et al. found that illicit use of pregabalin was common among opiate-addicted patients [13]. A study by Boden et al. investigating predictors of dosage above the maximum licensed dosage of pregabalin, found that patients with epilepsy and a diagnosis of addiction were more likely to receive pregabalin at higher dosages than recommended [14].

As pregabalin has been associated with abuse, we decided to investigate the trends in use of pregabalin in Denmark by using the extensive nationwide health registers. Additionally, we attempted to identify predictive variables for use of higher-than-recommended dosages.

Methods

Sample and subgroups

The study population consisted of all Danish users of pregabalin in the period from 2004 to 2013. Data was obtained from the nationwide Prescription Registry containing information on all prescription-based medications from all pharmacies in Denmark. The medication is registered according to the Anatomical Therapeutic Chemical (ATC) codes and amount is registered as defined daily dose (DDD) [15]. The ATC code for

received 04.09.2015
revised 18.01.2016
accepted 21.01.2016

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DOI http://dx.doi.org/10.1055/s-0042-101868
Published online: 2016
Pharmacopsychiatry

ISSN 0176-3679

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pregabalin is N03AX16 and one DDD is 300 mg. Indications and prescribed doses are not registered in the DRMPS. Instead we used ICD-10 diagnoses from the National Patient Registry and the Danish Psychiatric Central Research Register (DPCRR). These registers cover all admissions and outpatient contacts to all hospitals in Denmark, whereas diagnoses made by general practitioners (GP) are not included.

Temporal and geographical variation

We calculated the total number of users of pregabalin per year from 2004 until 2013 and the total annual amount of DDDs filled within the same period. The number of users in the 5 regions of Denmark was only estimated from 2008 to 2013, as prior to 2008 Denmark was constituted of counties instead of regions.

Lorenz curves and Gini coefficients

To demonstrate a possible skewed utilization pattern of pregabalin [16], we generated Lorenz curves on the total use of pregabalin for the year of 2013. Gini coefficient was calculated as a single measure indicating the skewness of the Lorenz curve [17].

Predictor variables of use of pregabalin at higher dosages

We used 2 models to assess excessive use of pregabalin; a short-term model and a long-term model. 2 outcomes were used for both models; daily use of more than 600 mg and daily use of more than 1 200 mg. In the short-term model we used a window of 6 months from each prescription until outcome criteria were fulfilled or 3 years after the first prescription of pregabalin. The long-term model was defined in a similar way but with a 1-year window from each prescription. The 6-month duration was chosen because of the constitution of the registers, as the prescription database contains no information on prescribed dosage or indication. Shorter periods are susceptible to errors as patients may pick up a large amount of medication, e. g., because they are going on vacation.

In this analysis, we included users filling their first prescription for pregabalin between inception in 2004 and December 31, 2010, in order to have at least 3 years of follow-up time (data was available until 2013). More than 600 mg per day was chosen as this reflects the maximum licensed dosage of 600 mg/day. More than 1 200 mg per day was used to reflect abuse as this dosage is unlikely to be prescribed for medical purposes.

We used the following explanatory variables: sex, age at first exposure to pregabalin, living alone and receipt of early retirement pension. Age at first exposure was divided into the following groups: < 20, 20–29, 30–39, 40–49, 50–59, 60–69 and > 70 years.

Additional explanatory variables were the following co-medication exposures in the 12 months prior to the first pregabalin prescription (ATC codes in parentheses): Antipsychotics (N05A minus N05AN01), antidepressants (N06A), opioids (N02A), antiepileptic (N03 minus N03AE01), psychostimulants (N06B), anticholinergics (N04A) and benzodiazepines not including benzodiazepine receptor agonists (N05BA, N05CD and N03AE01). Further, as antipsychotics are used for heterogeneous indications, we conducted univariate analysis for single antipsychotics used by at least 10 % of pregabalin users.

Statistical analysis

Epidemiological analysis was performed by using STATA version 13 and with remote access to Statistics Denmark. Temporal trends in the use of pregabalin were compared by using linear regression. A multiple logistic regression model was used to identify correlates of pregabalin use above the maximum licensed dosage.

Results

In total, we identified 80 868 patients, 31 612 males (39 %) and 49 256 females (61 %) exposed to at least one prescription of pregabalin within the period from 2004 to 2013. Median age at first exposure was 54 (IQR, 42–67) years. Among incident users of pregabalin, 29 % filled only one prescription (i. e., the index prescription) for pregabalin within the first 3 years of follow-up. Correspondingly, 12 % filled only one follow-up prescription, 7 % filled 2 follow-up prescriptions, while 51 % filled 3 or more follow-up prescriptions

Geographical variation and temporal trend in use of pregabalin

Annual numbers of pregabalin users increased linearly in the period from 1 765 in 2004 to 30 147 in 2013, as shown in **Fig. 1**. The number of pregabalin users per year in Denmark increased from 0.4 per 1 000 inhabitants in 2008 to 6.8 per 1 000 inhabitants in 2013. The incidence varied substantially from 4.2 per 1 000 inhabitants in 2013 in the Capital Region to 8.4 per 1 000 in the Mid Region as shown in **Fig. 2**. The median annual amount of DDD increased from 28 in 2005 to 112 in 2013, as shown in **Fig. 3**.

Lorenz curves and Gini coefficient

Lorenz curve of pregabalin use in 2013 is shown in **Fig. 4**. Gini coefficient was 0.582 and 1 % of users represented 6.1 % of total used amount. 50 % of users represented 91.3 % of the sold amount of DDD of pregabalin.

Factors associated with use of pregabalin above maximum licensed dosage

Out of 42 520 pregabalin users 4 090 (9.6 %) were treated with more than 600 mg/day for 6 months and 2 765 (6.5 %) for more than 12 months. 45 % were male and the median age was 49 years (interquartile range 38–59) in both the 6-month and 12-month group. In total 276 (0.65 %) were treated with more

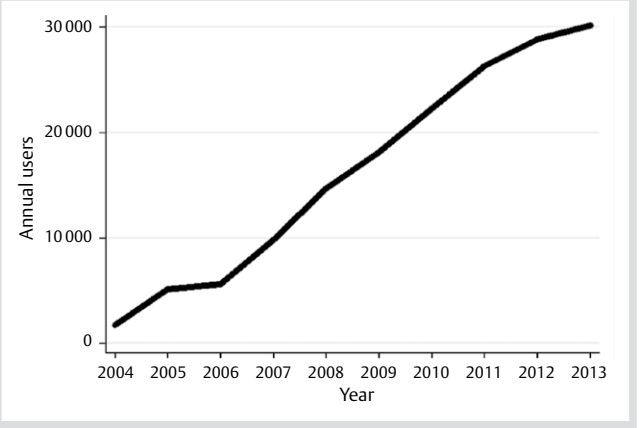

Fig. 1 Annual users of pregabalin in Denmark from 2004 to 2013.

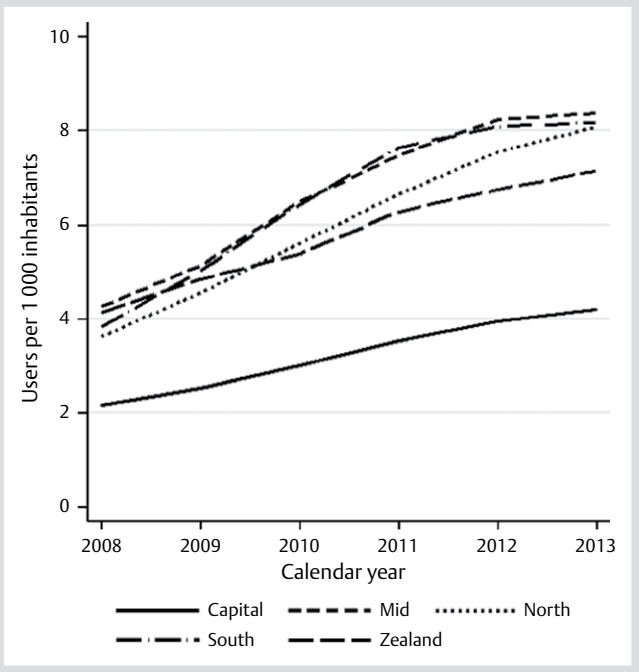

Fig. 2 Number of pregabalin users per 1 000 inhabitants from 2008 to 2013 in the 5 regions of Denmark.

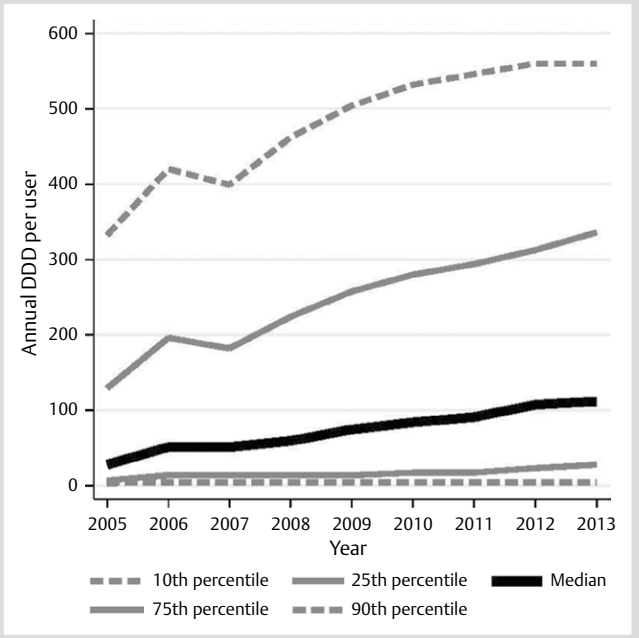

Fig. 3 Annual DDDs per user.

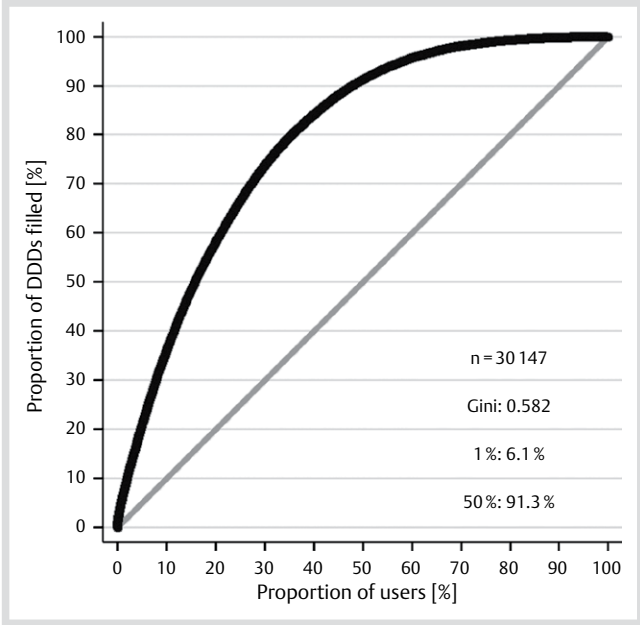

Fig. 4 Lorenz curve of pregabalin use.

than 1 200 mg in the 6-month model and 137 (0.33 %) in the 12-month model.

Male sex was associated with heavy use in both models and with both doses, as was early retirement pension, except in the adjusted long-term model with > 1 200 mg as the outcome variable as shown in **Tables 1,2**. Prescription of antipsychotic drugs and benzodiazepines was also associated with increased risk of being prescribed pregabalin in above-licensed doses in all analyses (a specification of antipsychotics is shown in **Table 3**). Prescription of other antiepileptic drugs was also associated with prescription of pregabalin in above-licensed doses in all analyses except for the adjusted analysis of the long-term model with 1 200 mg as the outcome variable.

In sensitivity analyses where we removed all users filling no or only one follow-up prescription for pregabalin, we obtained comparable results to those of the main analysis (data not shown).

Discussion

This is the largest and most comprehensive study to investigate the use of pregabalin from its introduction on the market in 2004 to the end of 2013. Our main finding was that 9.6 % and 6.5 % or individuals were prescribed more than 600 mg/day during a 6-month and a 12-month period, respectively. For doses above 1 200 mg/day the corresponding numbers were 0.6 % and 0.3 %. This suggests that pregabalin was not commonly prescribed in doses above the recommended or licensed dosages. A Lorenz-1 value of 6.1 % is not particularly indicative of high abuse potential although no clear cutoff value exits. Lorenz-1 values are normally above 10 % for drugs with high abuse potentials, such as strong opioids and benzodiazepines, and below 5 % for drugs with no or little abuse potentials, e.g., statins [17,18]. However, Lorenz curves estimate skewness of use at a population level. As such this analysis might not capture abuse in smaller vulnerable groups of patients and will not reflect recreational use of illegally obtained pregabalin.

During the study period the prescription rate of pregabalin increased dramatically as the number of users per 1 000 individuals increased linearly from 1 to 7. This trend is most likely explained by the extended indications for treatment with pregabalin. From the data available, we were not able to determine to what extent off-label use occurred.

We found a notable geographical variation of pregabalin prescription, with an apparently substantially lower utilization rate in Zealand Region compared to other regions in Denmark. Sociodemographics factors might contribute to these regional differences, although different therapeutic use of pregabalin between

Table 1 Predictors of pregabalin use of more than 600 mg/day.

	Short-term model (6 months)				Long-term model (12 months)			
	≥ 600 mg	<600 mg	OR single	OR multi	≥600 mg	<600 mg	OR single	OR multi
N	4090	38430	–	–	2765	39755	–	–
Male	1863 (45.6%)	14350 (37.3%)	1.40 (1.32–1.50)	1.43 (1.33–1.52)	1267 (45.8%)	14946 (37.6%)	1.40 (1.30–1.52)	1.42 (1.31–1.53)
Early retirement pension	1361 (33.3%)	8710 (22.7%)	1.70 (1.59–1.82)	1.27 (1.18–1.38)	953 (34.5%)	9118 (22.9%)	1.77 (1.63–1.92)	1.32 (1.20–1.45)
Living alone	1771 (43.3%)	15573 (40.5%)	1.12 (1.05–1.20)	1.04 (0.97–1.11)	1189 (43.0%)	16155 (40.6%)	1.10 (1.02–1.19)	1.02 (0.94–1.11)
Age (years)								
<20	12 (0.3%)	140 (0.4%)	0.80 (0.45–1.45)	0.73 (0.40–1.33)	8 (0.3%)	144 (0.4%)	0.80 (0.39–1.63)	0.73 (0.36–1.51)
20–29	374 (9.1%)	2048 (5.3%)	1.79 (1.59–2.01)	1.18 (1.03–1.36)	245 (8.9%)	2177 (5.5%)	1.68 (1.46–1.93)	1.13 (0.96–1.34)
30–39	740 (18.1%)	4498 (11.7%)	1.00 (ref.)	1.00 (ref.)	503 (18.2%)	4735 (11.9%)	1.00 (ref.)	1.00 (ref.)
40–49	998 (24.4%)	7094 (18.5%)	1.43 (1.32–1.54)	0.83 (0.75–0.93)	667 (24.1%)	7425 (18.7%)	1.38 (1.26–1.52)	0.83 (0.73–0.93)
50–59	970 (23.7%)	7833 (20.4%)	1.21 (1.13–1.31)	0.71 (0.64–0.79)	688 (24.9%)	8115 (20.4%)	1.29 (1.18–1.41)	0.75 (0.66–0.85)
60–69	685 (16.7%)	7344 (19.1%)	0.85 (0.78–0.93)	0.54 (0.48–0.60)	455 (16.5%)	7574 (19.1%)	0.84 (0.75–0.93)	0.54 (0.47–0.61)
70+	311 (7.6%)	9473 (24.7%)	0.25 (0.22–0.28)	0.25 (0.22–0.28)	199 (7.2%)	9585 (24.1%)	0.24 (0.21–0.28)	0.22 (0.19–0.27)
Region of residency								
North	489 (12.0%)	4182 (10.9%)	1.00 (ref.)	1.00 (ref.)	325 (11.8%)	4346 (10.9%)	1.00 (ref.)	1.00 (ref.)
Mid	1126 (27.5%)	9831 (25.6%)	1.11 (1.03–1.19)	0.92 (0.82–1.03)	807 (29.2%)	10150 (25.5%)	1.20 (1.10–1.31)	1.00 (0.87–1.15)
South	1059 (25.9%)	10008 (26.0%)	0.99 (0.92–1.07)	0.87 (0.78–0.98)	699 (25.3%)	10368 (26.1%)	0.96 (0.88–1.05)	0.87 (0.76–1.00)
Zealand	571 (14.0%)	6247 (16.3%)	0.84 (0.76–0.92)	0.75 (0.66–0.86)	388 (14.0%)	6430 (16.2%)	0.85 (0.76–0.94)	0.78 (0.67–0.92)
Copenhagen	830 (20.3%)	7340 (19.1%)	1.08 (1.00–1.17)	0.94 (0.83–1.06)	542 (19.6%)	7628 (19.2%)	1.03 (0.93–1.13)	0.93 (0.80–1.07)
Baseline use of drugs								
Antidepressants	2958 (72.3%)	23409 (60.9%)	1.68 (1.56–1.80)	1.38 (1.28–1.49)	1994 (72.1%)	24373 (61.3%)	1.63 (1.50–1.78)	1.35 (1.23–1.48)
Antipsychotics	1230 (30.1%)	6776 (17.6%)	2.01 (1.87–2.16)	1.46 (1.34–1.59)	836 (30.2%)	7170 (18.0%)	1.97 (1.81–2.14)	1.44 (1.30–1.59)
Benzodiazepines	1751 (42.8%)	13842 (36.0%)	1.33 (1.25–1.42)	1.20 (1.12–1.29)	1175 (42.5%)	14418 (36.3%)	1.30 (1.20–1.40)	1.16 (1.06–1.26)
Opioids	2285 (55.9%)	21750 (56.6%)	0.97 (0.91–1.04)	1.25 (1.16–1.34)	1566 (56.6%)	22469 (56.5%)	1.00 (0.93–1.09)	1.28 (1.18–1.39)
Antiepileptics	2025 (49.5%)	11827 (30.8%)	2.21 (2.07–2.35)	2.19 (2.05–2.34)	1385 (50.1%)	12467 (31.4%)	2.20 (2.03–2.37)	2.15 (1.99–2.33)
Psychostimulants	128 (3.1%)	710 (1.8%)	1.72 (1.42–2.08)	1.08 (0.88–1.32)	88 (3.2%)	750 (1.9%)	1.71 (1.37–2.14)	1.09 (0.87–1.38)
Anticholinergics	108 (2.6%)	432 (1.1%)	2.39 (1.93–2.95)	1.12 (0.89–1.41)	76 (2.7%)	464 (1.2%)	2.39 (1.87–3.06)	1.14 (0.88–1.48)

Table 2 Predictors of pregabalin use of more than 1 200 mg/day.

	Short-term model (6 months)				Long-term model (12 months)			
	≥ 1 200 mg	< 1 200 mg	OR single	OR multi	≥ 1 200 mg	< 1 200 mg	OR single	OR multi
N	276	42 244	–	–	137	42 383	–	–
Male	129 (46.7 %)	16 084 (38.1 %)	1.43 (1.13–1.81)	1.40 (1.10–1.78)	70 (51.1 %)	16 143 (38.1 %)	1.70 (1.21–2.38)	1.69 (1.20–2.38)
Early retirement pension	92 (33.3 %)	9 979 (23.6 %)	1.62 (1.26–2.08)	1.30 (0.98–1.73)	45 (32.8 %)	10 026 (23.7 %)	1.58 (1.10–2.26)	1.32 (0.89–1.97)
Living alone	135 (48.9 %)	17 209 (40.7 %)	1.39 (1.10–1.77)	1.17 (0.91–1.50)	66 (48.2 %)	17 278 (40.8 %)	1.35 (0.97–1.89)	1.17 (0.81–1.67)
Age (years)								
< 20	n < 5	148 (0.4 %)	4.18 (1.54–11.37)	2.91 (1.04–8.16)	n < 5	151 (0.4 %)	2.06 (0.29–14.80)	1.28 (0.17–9.45)
20–29	32 (11.6 %)	2 390 (5.7 %)	2.19 (1.51–3.17)	0.93 (0.61–1.42)	14 (10.2 %)	2 408 (5.7 %)	1.89 (1.09–3.29)	0.77 (0.42–1.42)
30–39	85 (30.8 %)	5 153 (12.2 %)	1.00 (ref.)	1.00 (ref.)	46 (33.6 %)	5 192 (12.3 %)	1.00 (ref.)	1.00 (ref.)
40–49	70 (25.4 %)	8 022 (19.0 %)	1.45 (1.10–1.90)	0.50 (0.36–0.70)	37 (27.0 %)	8 055 (19.0 %)	1.58 (1.08–2.30)	0.50 (0.32–0.77)
50–59	43 (15.6 %)	8 760 (20.7 %)	0.71 (0.51–0.98)	0.26 (0.18–0.38)	23 (16.8 %)	8 780 (20.7 %)	0.77 (0.49–1.21)	0.26 (0.16–0.44)
60–69	34 (12.3 %)	7 995 (18.9 %)	0.60 (0.42–0.86)	0.22 (0.15–0.34)	13 (9.5 %)	8 016 (18.9 %)	0.45 (0.25–0.80)	0.16 (0.08–0.30)
70 +	8 (2.9 %)	9 776 (23.1 %)	0.10 (0.05–0.20)	0.05 (0.02–0.10)	n < 5	9 781 (23.1 %)	0.07 (0.02–0.23)	0.03 (0.01–0.11)
Region of residency								
North	36 (13.0 %)	4 635 (11.0 %)	1.00 (ref.)	1.00 (ref.)	22 (16.1 %)	4 649 (11.0 %)	1.00 (ref.)	1.00 (ref.)
Mid	59 (21.4 %)	10 898 (25.8 %)	0.78 (0.59–1.04)	0.66 (0.43–1.00)	31 (22.6 %)	10 926 (25.8 %)	0.84 (0.56–1.26)	0.58 (0.33–1.01)
South	61 (22.1 %)	11 006 (26.1 %)	0.81 (0.61–1.07)	0.71 (0.47–1.08)	29 (21.2 %)	11 038 (26.0 %)	0.76 (0.51–1.15)	0.55 (0.32–0.97)
Zealand	48 (17.4 %)	6 770 (16.0 %)	1.10 (0.81–1.51)	0.92 (0.60–1.43)	24 (17.5 %)	6 794 (16.0 %)	1.11 (0.72–1.73)	0.75 (0.42–1.35)
Copenhagen	71 (25.7 %)	8 099 (19.2 %)	1.46 (1.11–1.91)	1.18 (0.78–1.77)	30 (21.9 %)	8 140 (19.2 %)	1.18 (0.79–1.77)	0.84 (0.48–1.46)
Antidepressants	195 (70.7 %)	26 172 (62.0 %)	1.48 (1.14–1.92)	1.09 (0.83–1.44)	98 (71.5 %)	26 269 (62.0 %)	1.54 (1.06–2.24)	1.18 (0.80–1.74)
Antipsychotics	98 (35.5 %)	7 908 (18.7 %)	2.39 (1.87–3.06)	1.69 (1.27–2.25)	47 (34.3 %)	7 959 (18.8 %)	2.26 (1.59–3.22)	1.61 (1.08–2.41)
Benzodiazepines	135 (48.9 %)	15 458 (36.6 %)	1.66 (1.31–2.10)	1.58 (1.22–2.04)	66 (48.2 %)	15 527 (36.6 %)	1.61 (1.15–2.25)	1.59 (1.10–2.30)
Opioids	170 (61.6 %)	23 865 (56.5 %)	1.24 (0.97–1.58)	1.91 (1.47–2.47)	88 (64.2 %)	23 947 (56.5 %)	1.38 (0.97–1.96)	2.19 (1.51–3.18)
Antiepileptics	135 (48.9 %)	13 717 (32.5 %)	1.99 (1.57–2.52)	1.90 (1.49–2.43)	57 (41.6 %)	13 795 (32.5 %)	1.48 (1.05–2.08)	1.38 (0.97–1.95)
Psychostimulants	11 (4.0 %)	827 (2.0 %)	2.08 (1.13–3.81)	1.08 (0.58–2.02)	n < 5	834 (2.0 %)	1.50 (0.55–4.06)	0.79 (0.29–2.17)
Anticholinergics	n < 5	538 (1.3 %)	0.57 (0.14–2.28)	0.22 (0.05–0.88)	n < 5	539 (1.3 %)	0.57 (0.08–4.09)	0.24 (0.03–1.74)

Table 3 Specification of antipsychotics associated with high use of pregabalin.

	Short-term model (6 months)			Long-term model (12 months)		
	≥ 600 mg	< 600 mg	OR	≥ 600 mg	< 600 mg	OR *
Levopromazine	210 (5.0 %)	967 (2.3 %)	2.22 (1.91–2.59)	148 (5.2 %)	707 (2.8 %)	1.90 (1.58–2.28)
Flupentixol	86 (2.0 %)	679 (1.6 %)	1.27 (1.01–1.59)	62 (2.2 %)	467 (1.8 %)	1.18 (0.90–1.54)
Chlorprothixene	470 (11.1 %)	1 922 (4.6 %)	2.61 (2.35–2.91)	316 (11.0 %)	1 494 (5.9 %)	1.98 (1.74–2.25)
Olanzapine	253 (6.0 %)	1 107 (2.6 %)	2.36 (2.05–2.71)	165 (5.8 %)	895 (3.5 %)	1.67 (1.41–1.98)
Quetiapine	458 (10.8 %)	2 119 (5.0 %)	2.29 (2.06–2.55)	314 (11.0 %)	1 680 (6.6 %)	1.74 (1.53–1.97)
Risperidone	192 (4.5 %)	1 022 (2.4 %)	1.91 (1.63–2.24)	122 (4.3 %)	796 (3.1 %)	1.37 (1.13–1.67)
Paliperidone	130 (3.1 %)	540 (1.3 %)	2.44 (2.01–2.96)	89 (3.1 %)	449 (1.8 %)	1.78 (1.41–2.24)
	≥ 1 200 mg	< 1 200 mg	OR	≥ 1 200 mg	< 1 200 mg	OR *
Levopromazine	22 (7.7 %)	833 (3.0 %)	2.73 (1.76–4.24)	10 (7.2 %)	845 (3.0 %)	2.52 (1.32–4.81)
Flupentixol	8 (2.8 %)	521 (1.9 %)	1.52 (0.75–3.10)	n < 5	526 (1.9 %)	1.16 (0.37–3.67)
Chlorprothixene	44 (15.5 %)	1 766 (6.3 %)	2.72 (1.96–3.76)	23 (16.7 %)	1 787 (6.4 %)	2.94 (1.88–4.61)
Olanzapine	17 (6.0 %)	1 043 (3.7 %)	1.64 (1.00–2.69)	12 (8.7 %)	1 048 (3.7 %)	2.46 (1.35–4.45)
Quetiapine	39 (13.7 %)	1 955 (7.0 %)	2.11 (1.50–2.97)	19 (13.8 %)	1 975 (7.0 %)	2.11 (1.30–3.43)
Risperidone	12 (4.2 %)	906 (3.2 %)	1.32 (0.74–2.35)	n < 5	914 (3.3 %)	0.89 (0.33–2.40)
Paliperidone	9 (3.2 %)	529 (1.9 %)	1.69 (0.87–3.31)	n < 5	536 (1.9 %)	0.76 (0.19–3.06)

*) Univariate logistic regression

Copenhagen and the rest of Denmark are likely the most prominent cause. All the remaining 4 regions in Denmark had a comparable use. Similar geographical variation in Denmark has been documented for other psychotropic drugs, such as clozapine [19] and ADHD medications [20,21]. Overall, Denmark is quite homogenous in terms of demographics, health care utilization and use of prescription drugs [22]. Unfortunately, we were not able to separate use on a regional level before 2008 because the regions were first established in that year. However, based on the slopes in **Fig. 2**, the relevance of this is most likely minor.

In all models, male sex and age between 20–40 years were independent risk factors for receiving prescriptions of pregabalin at higher dosages than recommended. Both of these findings are in line with previous results [14]. Use of opioids was also associated with increased risk of high-dose pregabalin in all models. The latter observation may reflect several scenarios. Firstly, it may reflect the analgesic effects of pregabalin, which may augment the effect of opioids [23]. Secondly, it may also reflect the use of pregabalin for reducing withdrawal symptoms from opioids [24]. During this augmentation or withdrawal process patients may be more likely to ingest higher dosages of pregabalin. Thirdly, it may also confirm the finding by Grosshans et al., where pregabalin was more common among opiate-addicted patients, who may be more likely to be prescribed both pregabalin and opiates [13]. Prescription of benzodiazepines was associated with increased risk of high use pregabalin. One reason might be that the constant focus on reducing the use of benzodiazepines has shifted the demand to other psychotropic drugs with anxiolytic properties, such as pregabalin [25]. Although some evidence suggests a role for pregabalin in withdrawal from benzodiazepines, more high-level evidence is warranted before any clinical recommendations can be made [26]. In particular, we believe that the cognitive adverse effects of pregabalin and benzodiazepines should be compared. The weight gain potential of pregabalin should be given appropriate attention in the evaluation of whether pregabalin should replace long-term benzodiazepine use [27]. Interestingly, use of antipsychotic drugs was also associated with high use of pregabalin. Especially antipsychotic drugs with high sedative effects, such as chlorprothixene, levomepromazine, olanzapine and quetiapine, were associated with high use. As these antipsychotic drugs are used for anxiolytic treatment this may also be a result of the increased focus on reducing use of benzodiazepines.

We found high use of pregabalin to be associated with the use of other drugs with known abuse potential, like opioids and benzodiazepines. This finding is in line with published case reports describing abuse of pregabalin among patients with known substance abuse disorder [28,29]. In some cases pregabalin is used to achieve euphoric effects similar to alcohol or benzodiazepines [9,12] which may be a precursor to dependency [30]. This is in contrast to several animal studies that failed to show rewarding properties of pregabalin alone [31,32].

Our study should be interpreted within its limitations. Pregabalin was mostly prescribed by general practitioners, and diagnoses or indications for treatment in this primary care setting are not available in national registries. We used co-prescription of other medications as markers for such comorbidity; however, psychotropic drugs are used for several reasons, complicating further interpretations. Use of medications, including pregabalin, was based on the Danish Register of Medicinal Products Statistics (DRMPS), which covers all medications picked up from pharmacies. DRMPS does not include medications during inpatient status, and for long-term inpatients this may have resulted in underestimated dosages since the hospital provides the medication during inpatient status. However, long-term admission is considered rare among this patient group.

We were not able to assess compliance and it cannot be confirmed that the patient who picked up the prescription was actually the one taking the medicine. Diversion of pregabalin, i.e., illicit channelling of regulated pharmaceuticals from legal sources to the illicit marketplace, may happen but it is unclear to what extent. Recreational use and diversion of pregabalin has been described in case reports [12,33] and in epidemiological studies [34]. As these patients may have pregabalin prescribed in recommended doses, the signal of pregabalin abuse might be underestimated. Unfortunately it is not possible to adjust for diversion in drug utilization studies such as this.

Based on the data from Danish nationwide health registers, we conclude that use of pregabalin in Denmark increased 7-fold from its inception in 2004 to 2013. Use of pregabalin in doses above the licensed marketing authorization is uncommon. However, treating physicians should pay special attention to signs of

abuse when prescribing pregabalin to patients already receiving benzodiazepines, antipsychotics or opioids.

Conflict of Interest

OIe Schjerning has received speakers honoraria from Lundbeck. Jimmi Nielsen has received research grants from Lundbeck, Pfizer and speakers honoraria from Hemocue, Lundbeck and Bristol Myers Squibb. Anton Pottegård, Mary Rosenzweig and Per Damkier state no conflict of interest.

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