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Abstract

Purpose: Pregabalin is a gamma-aminobutyric acid (GABA) analogue approved for the treatment of epilepsy, neuropathic pain, and generalised anxiety disorder. As a GABA analogue, there has been some concern about an abuse liability. We aimed to investigate the possible abuse liability of pregabalin. **Methods:** By applying a Bayesian data-mining algorithm to reports of possible drug abuse or addiction in the Swedish national register of adverse drug reactions (SWEDIS), we calculated the information component (IC) for pregabalin and reports of abuse and addiction. **Results:** Out of 198 reports indicative of abuse or addiction to any drug, sixteen concerned pregabalin. The IC became significantly elevated in the fourth quarter of 2008, rising to 3.99 [95% confidence interval 3.21-4.59] at the end of 2009. **Conclusion:** Based on the signal from the present study, we conclude that pregabalin is likely to be associated with an abuse potential.

Keywords

Pregabalin, abuse, addiction, adverse drug reaction, data-mining.

Introduction

Pregabalin is a gamma-aminobutyric acid (GABA) analogue used for the treatment of epilepsy, neuropathic pain, and generalised anxiety disorder (GAD) (1). Although its precise mechanism of action is unclear, pregabalin decreases central neuronal excitability by binding to an auxiliary subunit (α_2-δ protein) of a voltage-gated calcium channel on neurons in the central nervous system and reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P.

In the European Union as well as in the US, pregabalin was first approved for the treatment of epilepsy and peripheral neuropathic pain (1). As a GABA analogue, there was some concern about a potential for addiction and drug abuse (1). Premarketing trials had produced somewhat conflicting results in this respect. Studies in vitro did not show that the drug or its metabolites interacted with $GABA_A$ or $GABA_B$ receptors or inhibited GABA uptake or degradation, and studies in rats and monkeys found no propensity for an abuse liability although modest withdrawal signs upon discontinuation was observed in rats (1). In addition, a dedicated clinical study in 15 recreational alcohol/sedative users found pregabalin in therapeutic doses of 200-450 mg not to produce the same responses as diazepam, indicating that the drug did not have the profile of a prototypic drug of abuse, although it did produce subjective effects on a wide variety of measures that were different from placebo (1). Consequently, the potential for drug abuse or physical dependence for pregabalin was assessed as low at the time of marketing authorisation (1). It was noted, however, that euphoria occurred as an adverse event in clinical trials among 1-10% of patients depending on dose, compared with 0.5% for placebo (1). Other adverse events such as depersonalisation,

nervousness, abnormal thinking and amnesia, symptoms which may reflect benzodiazepine-like adverse events, were also observed (1).

In later clinical trials in patients with central neuropathic pain and in patients with GAD, euphoria as an adverse event was also reported as common for pregabalin (1), and assessments of withdrawal symptoms in clinical trials of GAD showed a profile similar to lorazepam (1), especially in the 600 mg/day dosage. There was, however, no indication of significant dose escalation in open-label trials (1).

An essential feature for effective risk management for drugs with an uncertain abuse liability is post-marketing surveillance that can detect the emergence of an abuse problem before the abuse of the medication becomes a major public health problem. Addiction is not labelled in the European Summary of Product Characteristics (SPC) for pregabalin but is included as a rare adverse drug reaction (ADR) in the US label (2,3). As the question of a possible abuse potential for pregabalin is currently unsolved, we conducted a database analysis of reports of possible drug abuse or addiction to pregabalin in the Swedish national register of adverse drug reactions (SWEDIS) (4).

Material and method

At the end of 2009, SWEDIS contained some 100000 spontaneous reports submitted since 1965 by Swedish physicians to the Swedish Medical Products Agency (MPA). A Swedish dictionary is used for coding ADRs, built on a three-level hierarchical structure developed by the MPA (4). The first level is the system organ class, followed by group terms, and finally preferred terms. The dictionary holds a little over 1000 preferred terms. The information in a

report consists of patient demographics, reported ADRs, medication and a case narrative, often accompanied by copies of medical charts. All reports are reviewed by the MPA and a causality assessment is made, i.e., medicines can be listed as being suspected of having caused the reaction or as concomitant medication not related to the ADR. Drugs are coded with the WHO Collaborating Centre for Drug Statistics Methodology international anatomical therapeutic chemical (ATC) classification (5). To assess whether cases of possible drug abuse or addiction to pregabalin have been more commonly reported than expected, we calculated the information component (IC) (6) for the preferred terms "addiction", "drug addiction", "dependence", "tolerance increased", and "drug abuse" as a group. As some reports indicative of abuse may sometimes be coded with the terms "intoxication", "overdose", or "pathological inebriation", we also manually scanned all such reports for every drug in SWEDIS (n=718, of which 9 included pregabalin as suspected drug) and included such reports in the calculations. In this respect, we only included reports in which the reporting physician had clearly stated that the patient had abused the suspected drug. The IC is a logarithmic measure of association derived from a Bayesian data-mining algorithm used commonly in pharmacovigilance practise for the detection of potential safety signals (6). An IC of 0 results from drug-event combinations for which the number of observed cases is the same as that which might be expected from the overall reporting in the data set. Positive values represent combinations reported more frequently and negative values more infrequently than expected. Confidence intervals (CIs) of the IC (IC ±2 standard deviations) are calculated to account for sampling variability. We have previously shown that this methodology can be applied to SWEDIS with a near 80% probability for signalled drug-event combinations to be currently labelled (4). As reports before 1980 often contained only limited information, we restricted the analysis to reports entered into the database from 1980 until the end of 2009. As a significant proportion (15%) of the reports concerned ADRs from vaccines (ATC class J07) and since such

medicinal products are not associated with an abuse potential, we excluded these from the data set. All statistical calculations were performed in Microsoft Excel 2007 (Microsoft Corporation).

Results

Out of 82714 reports in SWEDIS during the study period, a total of 198 reports indicative of abuse or addiction to any drug were identified, of which 16 concerned pregabalin (tables 1 and 2). Three of the reports for pregabalin were received from the same reporter, and the other 13 from single reporters across Sweden. The evolution of the IC with 95% CI over time for pregabalin is shown in figure 1. The first reports were received in the first quarter of 2008, and the IC first became significantly elevated in the fourth quarter of 2008 with four reports entered into SWEDIS (IC=2.38 [95% CI 0.70, 3.50]), rising to 3.99 [3.21-4.59] at the end of 2009 on the basis of 16 reports. An overview of relevant data from these reports can be found in table 3. The median age of the patients was 29 years (range 18-51, age unknown for one case) and included 9 males and 7 females. The reported maximum daily doses ranged from 300-4200 mg (median 1000 mg), mostly taken as single doses. Six reports were coded as "drug abuse" and included one patient who injected pregabalin after dissolving the substance in water, and one patient who nasally inhaled the drug after crushing the contents of the capsules. Feelings of becoming "high" or of "a nice bensodiazepine effect" were described. Four reports were coded as "intoxication", in which patients reported having taken pregabalin to "get high" or described an effect similar to an "amphetamine trip" with euphoria. Two reports were coded as "dependence" and described feelings of being "high" and hospitalisations for detoxification. Two reports were coded as "tolerance increased" where patients increased their doses above the maximum recommended (1200 and 3000 mg/day)

due to waning of effect. One report was coded as “drug addiction” in which the patient described a feeling of becoming “high” with a sensation of flying. The last case was coded as “pathologic inebriation” in which the patient reported using pregabalin to potentiate the effect of alcohol. Out of the 16 cases, thirteen included a history of past or current substance abuse, and two patients reported selling part of their prescribed medication on the black market. The indication for which pregabalin had been prescribed was mostly unknown, but was reported as non-specified anxiety in five cases, and non-specified pain and GAD in one case.

Discussion

This is the first post-marketing study to show a signal of an abuse liability for pregabalin. As is common for a drug with an abuse liability, risk factors include a history of substance abuse, which was present in 13/16 of the reports in SWEDIS. With a structure and pharmacodynamic profile similar to pregabalin, gabapentin would also be expected to exhibit a similar signal. However, we have found no case indicative of abuse or addiction to gabapentin in SWEDIS (data not shown). This difference may be due to pharmacodynamic differences, differences in reporting propensity or differences in the indications for use. Pregabalin is approved for the treatment of GAD, whereas gabapentin is not (7), and while the indication for use was mostly unknown for the 16 cases described herein it is of note that anxiety was the reported indication among the six cases where such information was provided, suggesting an association between abuse liability and indication as has been described previously (8).

Some limitations with signals derived from data-mining studies should be discussed. Data-mining methods in pharmacovigilance practices provide signals and not evidence of safety problems (6). Thus, the present finding of a possible abuse liability for pregabalin should be considered as a signal which needs further testing in other materials. A potential source of

bias is media attention concerning the drug-event combination in question, i.e. media attention may stimulate reporting, resulting in exaggerated signals. However, there have been no such attention regarding pregabalin and abuse in Sweden during the covered period of the present study, nor any communications from regulatory authorities of such a potential. Another conceivable source of bias is when a drug is often co-prescribed with another drug which in turn is strongly associated with a particular ADR. In this situation, the drug under study may be suspected to cause the ADR, when it in fact is an innocent by-stander. In the present study, however, pregabalin was the only suspected drug in 13/16 cases, thereby rendering this possibility unlikely. Under-reporting of ADRs indicative of abuse might also introduce bias if this is selective for some drugs, e.g., for older drugs as compared to newer. It is not possible to fully exclude such a possibility, but it would seem unlikely that this type of bias would result in a steadily increasing signal as presented in this report.

Conclusion

In Sweden, use of pregabalin is rapidly increasing and was 9.3 million DDDs in 2009, compared with 4.6 million in 2007. Based on the signal from the present study, we conclude that pregabalin is likely to be associated with an abuse liability and that further studies are urgently needed to characterise its extent and nature.

Conflicts of interest

All authors declare no conflicts of interest. No funding source was involved in this study.

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Adverse event term	Pregabalin	All other drugs
Drug addiction	1	6
Dependence	2	91
Tolerance increased	2	20
Drug abuse	6	0
Addiction	0	59
Intoxication	4	6
Overdose	0	5
Pathological inebriation	1	0
Total number of unique reports indicative of abuse*	16	182
Number of other reports	210	82306
Total number of reports in SWEDIS	226	82488

Table 1. Number of drug-event combinations and reports indicative of possible abuse in SWEDIS between 1980-2009 for pregabalin and all other drugs (ATC class J07, vaccines, removed).

* As each report may contain more than one adverse event term, the total number of unique reports indicative of abuse may be less than the total number of adverse events.

Drug	Dependence	Drug addiction	Tolerance increased	Addiction	Intoxication	Overdose	Total
Tramadol	1	39	15	27	0	0	82
Bensodiazepine-like drugs*	2	34	5	16	4	1	62
Bensodiazepines	2	12	1	8	0	1	24
Codeine	0	7	5	10	0	2	24
Carisoprodol	0	5	0	0	0	0	5
Anti-parkinsonian drugs	1	0	0	2	1	0	4
Dextropropoxyphene	0	2	1	0	1	0	4
Nicotine	0	2	0	1	0	1	4
Amphetamine	2	1	0	0	0	0	3
Baclofen	0	3	0	0	0	0	3
Triptanes	0	1	0	1	0	0	2
Morphine	0	2	0	0	0	0	2
Buprenorphine	0	1	0	1	0	0	2
Ketobemidone	0	0	1	1	0	0	2
Neuroleptics	1	0	0	0	0	0	1
SSRI/SNRI	0	1	0	0	0	0	1
Estriol	0	1	0	0	0	0	1
Oxycodone	0	0	0	1	0	0	1
Barbiturates	0	0	0	1	0	0	1
Meprobamate	0	0	0	1	0	0	1
Total	9	111	28	70	6	5	229

Table 2. Number of drug-event combinations indicative of abuse for all drugs other than pregabalin in SWEDIS between 1980-2009 (ATC class J07, vaccines, removed). The total number of unique reports are 182. Note that the number of drug-event combinations is greater than the number of unique reports as each report may contain several suspected drugs. There were no events coded as ”drug abuse” for these drugs, nor any case of ”pathologic inebriation” indicative of abuse.

* Zolpidem, zopiclone and zaleplon.

Report #	Time of report	ADR term	Age (years)	Sex	Highest daily dose (mg)	Indication	Time to onset	Other suspected drugs	Concomitant drugs	Brief narrative	History
1	2009Q4	Intoxication	28	Female	Unknown	Unknown	Unknown	None	Unknown	Patient took pregabalin to "become high". Mixed 3 bottles of beer with pregabalin. Developed psychotic reaction, walked in snow bare-footed leading to frostbite.	Social situation problematic. Previous history of abuse (amphetamine, extacy).
2	2008Q1	Intoxication	43	Female	1000	Unknown	Unknown	Oxazepam, propiomazine, zolpidem	Alimemeazine, valproic acid, venlafaxine	Patient developed euphoria, hyperactivity, described as an "amphetamine trip". Decreased consciousness when mixed with propiomazine and zolpidem.	Current history of abuse to bensodiazepines.
3	2008Q4	Intoxication	18	Male	875	Unknown	Unknown	None	Mirtazapine	Patient took pregabalin to "become high". Developed generalized seizures.	ADHD. Previous abuse of tramadol and alchohol.
4	2008Q3	Intoxication	35	Female	525	Anxiety (non-specified)	Unknown	None	Zolpidem, diazepam, acetylsalicylic acid, caffeine, codeine	Described as an "amphetamine trip", developed euphoria.	History of abuse of bensodiazepines, acetylsalicylic acid, amphetamine.
5	2008Q1	Drug addiction	23	Male	300	Unknown	Unknown	None	None	Patient described a feeling of being "high", and felt as if flying.	History of abuse of non-specified substances.
6	2008Q4	Dependence	38	Female	600	Anxiety (non-specified)	Unknown	None	Drospirenon/ethinylestradiol, fluoxetine	Patient described a feeling of "becoming high" and that pregabalin felt like "a drug". Developed euphoria, impaired judgement leading to problems at work, withdrawal reaction requiring hospitalisation.	Unknown
7	2009Q3	Dependence	26	Male	2400	Anxiety (non-specified)	About 1 year	None	None	Hospitalisation for detoxification.	History of abuse of bensodiazepines, amphetamine and cannabis.
8	2009Q1	Tolerance increased	26	Female	1200	Anxiety (non-specified)	About 2 months	None	None	Slow tapering of dose required.	History of non-specified substance abuse.
9	2009Q1	Tolerance increased	38	Male	3000	Anxiety (non-specified)	About 3 months	None	Duloxetine	Patient increased dose himself due to worsening of anxiety. Thoughts of suicide when trying to lower dose. Required slow tapering of the dose.	History of non-specified substance abuse. History of anxiety and depression.
10	2009Q3	Drug abuse	51	Male	Unknown	Unknown	Unknown	None	Esomeprazole, clomipramine, carbamazepine	Large consumption of pregabalin leading to amnesia and thoughts of suicide.	History of abuse of alcohol, opioids and cannabis.
11	2009Q3	Drug abuse	29	Male	Unknown	Unknown	Unknown	Alprazolam	None	Unknown	History of abuse of heroin and other non-specified substances. Current history of abuse of alprazolam, heroin, alcohol.
12	2009Q4	Drug abuse	32	Male	Unknown	Unknown	Unknown	Zolpidem	None	Multiple hospital admissions due to abuse of pregabalin and zolpidem. Pregabalin was dissolved in water and injected, or combined with bensodiazepine for "increased effect". Patient sold his pregabalin tablets.	History of abuse of zolpidem and other non-specified substances.
13	2009Q4	Drug abuse	42	Female	4200	Unknown	10 days	None	Zolpidem, naltrexone, oxazepam, zopiclone, olanzapine	Patient expected "a state of intoxication". Developed psychosis requiring hospitalisation.	History of non-specified substance abuse, and paranoid schizophrenia.
14	2009Q4	Drug abuse		Male	1050	Non-specified pain and generalised anxiety disorder	1 week	None	None	Patient experienced "a nice benso-effect". Emptied pregabalin capsules and filled them with salt, tried to return them in exchange for new.	Unknown
15	2009Q4	Drug abuse	19	Male	300	Unknown	Unknown	None	None	Patient took pregabalin to "get high". Described an effect similar to that of "massive doses of diazepam". Doses were crushed and inhaled nasally,	History of ADHD and anxiety.
16	2009Q4	Pathologic inebriation	29	Female	Unknown	Unknown	Unknown	None	None	Patient described an increased effect of alcohol. Combined use of pregabalin and alcohol led to "increased effect of alcohol". Behavioural disturbances, including borrowing a car without permission and driving under the influence. Patient sold part of her pregabalin capsules on the black market.	History of abuse of amphetamine, alcohol and bensodiazepines.

Table 3. Description of the 16 cases in SWEDIS up to the 4th quarter (Q) of 2009 indicative of abuse of pregabalin.

ADR=adverse drug reaction; ADHD=Attention-Deficit/Hyperactivity Disorder.

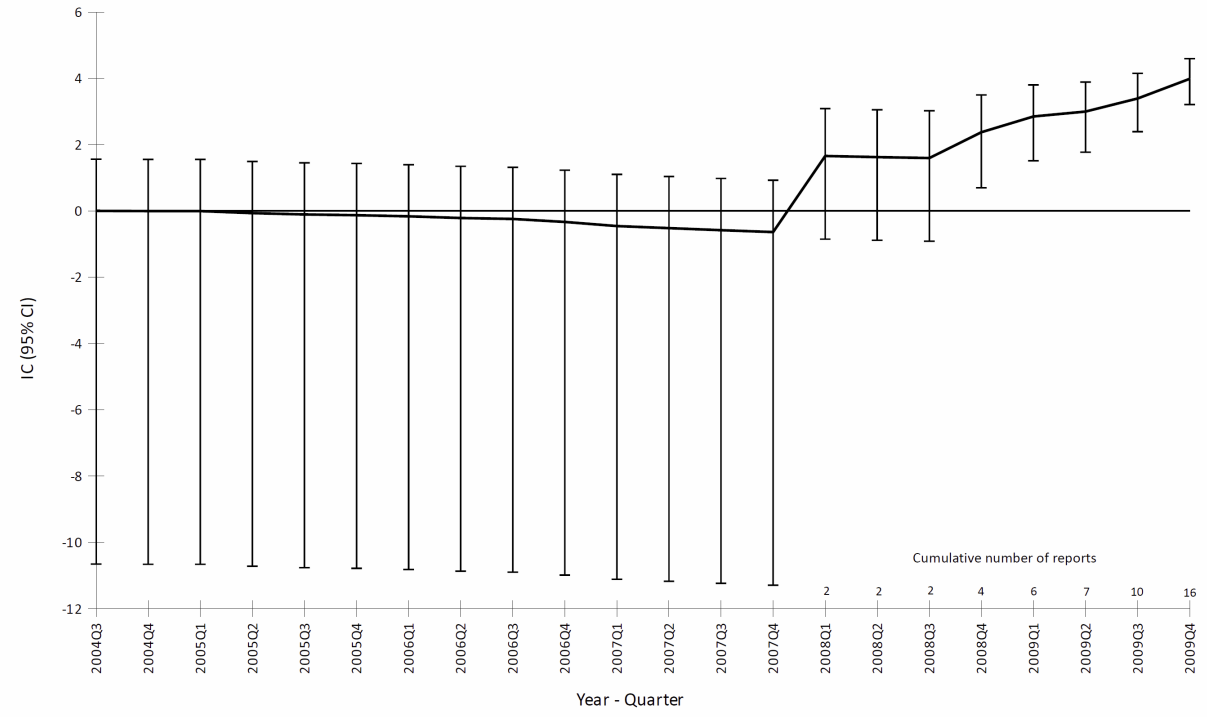

Figure 1. *Evolution of the information component (IC) for reports of suspected abuse or addiction to pregabalin.* The figure shows the IC with 95% confidence interval (CI) per quarter (Q) of year for reports of suspected abuse or addiction to pregabalin in the Swedish national register of adverse drug reactions (SWEDIS), first becoming significantly elevated in 2008Q4. Calculations are based on reports in SWEDIS between 1980-2009, with reports for ATC class J07 (vaccines) removed. Also shown are the cumulative number of reports of suspected abuse or addiction to pregabalin per quarter of year (first reports received in 2008Q1).