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Intensive Monitoring of Pregabalin

Results from an Observational, Web-Based, Prospective Cohort Study in the Netherlands Using Patients as a Source of Information

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Abstract

Background: Pregabalin is one of the first drugs registered for the treatment of neuropathic pain. It is also indicated as adjuvant therapy in the treatment of epilepsy and for generalized anxiety disorder. Pregabalin is a GABA analogue and exerts its effect by binding to the α_2-δ subunit of voltage-gated calcium channels, leading to a decreased synaptic release of neurotransmitters.
Objective: To gain insight into the safety and user profile of pregabalin in daily practice, reported by patients via a web-based intensive monitoring system based at the Netherlands Pharmacovigilance Centre Lareb.
Methods: Lareb Intensive Monitoring is an observational prospective cohort study with no limiting inclusion or exclusion criteria compared with clinical trials. First-time users of pregabalin were identified through the first prescription signal in intensive monitoring participating pharmacies between 1 August 2006 and 31 January 2008. Eligible patients received information about the pregabalin study in the pharmacy. When registering online, patient characteristics and information about pregabalin and other concomitant drug use were collected. After registration, the patient received questionnaires by e-mail 2 weeks, 6 weeks, 3 months and 6 months after the start of pregabalin. In these questionnaires, possible adverse drug reactions (ADRs) were addressed. Reactions not labelled in the Summary of Product Characteristics of pregabalin, and reactions that were labelled but were interesting for other reasons, were analysed on a case-by-case basis.
Results: In total, 1373 patients filled in the online registration form. The average age of participants was 54.5 years (range 11–89), with 58.0% being female. The indication for pregabalin use was neuropathic pain in 85.9% of participants. The average daily dose was 201 mg, and 80.5% of all users used pregabalin capsule 75 mg. All patients who registered for the study were sent a questionnaire; 1051 (76.5%) patients filled in at least one questionnaire. There were no statistically significant differences found regarding sex, age or

daily dosage between this latter group compared with the patients who registered for the study but did not fill in a questionnaire.

At least one possible ADR was reported by 69.3% of patients and serious ADRs were reported by 11 patients. The five most frequently reported possible ADRs were dizziness, somnolence, feeling drunk, fatigue and increased weight. Four associations were further analysed. Headache was analysed because of its high frequency. The time to onset ranged from a few hours to 5 months, with a median time to onset of 2 days. In 15 reports the headache passed without withdrawing the drug, and in ten cases the headache disappeared after drug withdrawal. Upper abdominal pain, a possible drug interaction between pregabalin and blood glucose-lowering agents, and suicidal ideation were considered to be signals.

Conclusions: Web-based intensive monitoring is an observational prospective cohort study. It will therefore provide a picture of the use of pregabalin and its ADRs in daily practice. This study indicates that pregabalin is a relatively safe drug. Eleven patients (<1.0%) experienced a serious ADR while using the drug. The most frequently reported possible ADRs correspond with the reactions most frequently reported during clinical trials.

The study demonstrates that a web-based intensive monitoring system can contribute to greater knowledge about a reaction, such as headache, with quantification and information about latencies and time course of the reaction. It can also detect signals worth further investigation, such as abdominal pain and possible interaction with oral antidiabetics.

Background

Neuropathic pain is pain associated with disease or injury of the peripheral or central nervous system.[1] This type of pain is considered to be particularly difficult to treat.[2] In the Netherlands, the incidence rate of neuropathic pain has been estimated to be 8.2 per 1000 person-years, translating to 0.8% of the population per year, or more than 130 000 new cases yearly. Neuropathic pain is more common in women than in men (63% of all patients with neuropathic pain are female) and peaks between the ages of 70 and 79 years.[3]

Antiepileptics (such as gabapentin and carbamazepine) and antidepressants (such as nortriptyline and amitriptyline) have been shown to be effective in treating neuropathic pain.[4] In 2004, pregabalin was introduced in Europe for the treatment of neuropathic pain. In addition to neuropathic pain, pregabalin is also indicated as adjuvant therapy in the treatment of epilepsy and for generalized anxiety disorder.[5] It is a GABA analogue and exerts it effects by binding to the α_2-δ subunit of voltage-gated calcium channels, leading to a decreased synaptic release of neurotransmitters.[6] Before pregabalin approval, its efficacy had been investigated in more than ten controlled clinical trials, none of which lasted longer than 13 weeks.[5] Because of the well known limitation of premarketing studies,[7] the full benefit-risk balance and user profile of pregabalin could not be considered to be complete at the time of marketing. Monitoring of the drug in daily practice is therefore necessary.

The main method of gathering data in the postmarketing phase is through a spontaneous reporting system,[8] whereby healthcare professionals and, increasingly, patients can submit reports of adverse drug reactions (ADRs). These reports can lead to the detection of a new signal,

an association between a drug and an ADR, previously not known. Even though spontaneous reporting has shown its strengths throughout the years,[9] it also has limitations. One of the most frequently mentioned is underreporting[10] and the inability to assess the incidence of the reported ADRs.

Spontaneous reporting systems focus on detecting new signals. The detection of a new signal is not always sufficient for a well informed decision to be made as to whether to use that drug or not. Information on who is at risk of developing the ADR, the latency, duration, seriousness and severity of the ADR, and what action is necessary to cope with the ADR, is information that can help in the decision-making process. Traditionally, pharmacovigilance has been focused on finding unrecognized potential harm that has not yet been demonstrated. Waller and Evans[11] have suggested that pharmacovigilance should be less focused on finding harm and more focused on extending knowledge of safety. Extending knowledge on safety is difficult since safety can only be demonstrated to a finite degree.[11] In terms of demonstrating safety, new forms of postmarketing research are needed to gather information that aims to provide information on safety instead of focusing on finding harm, for example observational cohort studies.

In the Netherlands, the Netherlands Pharmacovigilance Centre Lareb has been responsible for the collection and analysis of spontaneous reports since 1995. To meet the increasing needs of extending the knowledge about the use and safety of a drug in daily practice, a new method has been developed. In spontaneous reporting a report is only submitted when the patient has experienced an ADR. This new method is focused on gathering information on safety from the patient's first day of use of a specific drug. Some patients might experience a possible ADR and some might not, and by monitoring all first-time users of a drug it will be possible to gather information from daily practice. In 2006, a web-based intensive monitoring system, called Lareb Intensive Monitoring (LIM), was introduced. This system is based on patients filling in questionnaires sent by e-mail during the first period of time that they use the drug.[12-14]

The aim of this study is to gain insight into the user profile and safety of pregabalin in daily practice, reported by patients via a web-based intensive monitoring system during the first 6 months of use.

Method

Study Population

The included population consisted of first-time users of pregabalin, identified through the first prescription signal in the intensive monitoring participating pharmacies between 1 August 2006 and 31 January 2008. Data were collected between 1 August 2006 and 31 July 2008.

Community pharmacists were invited to participate in the intensive monitoring system, and more than 1000 pharmacies (more than 50% of all Dutch pharmacies) decided to participate. Patients in the Netherlands are linked to one pharmacy only, which makes it possible to monitor a patient's drug use. The computer can signal if a patient is receiving a drug for the first time, i.e. the patient has not filled a prescription for the drug, in that particular pharmacy, in the previous 12 months. The pharmacist receives a special LIM signal when a drug studied with the LIM system is dispensed for the first time. If receiving pregabalin for the first time, patients receive information in the pharmacy about the pregabalin study and are given a pharmacy-specific code with which they can sign up for the study online.

Data Collection

Upon registration, patients were asked for an e-mail address, which was used for further correspondence. Patient characteristics such as sex, birth date, height and weight were collected. Information about pregabalin use, including start date, strength, product code, dosage, administration form and indication were collected. This information was also gathered for all concomitant medication. Patients received questionnaires by e-mail 2 weeks, 6 weeks, 3 months and 6 months after starting to take the drug. These questionnaires collected information on possible ADRs: seriousness of the reaction according to the criteria developed by CIOMS, which include

(prolongation of) hospitalization, life-threatening events, reactions leading to death, disabling events, congenital abnormalities and other medically important conditions; start date of reaction; action taken with pregabalin (stopping/dose reduction/no dose change); and outcome of the reaction. For an overview of the questionnaires see tables SI and SII, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A38. If the patient did not fill in the questionnaire immediately, a reminder was sent 5 days later. If a questionnaire was not completed 4 weeks after the reminder, the patient was considered 'lost to follow-up' for that questionnaire.

If the patient stopped the use of pregabalin, or in the event of death of the patient or if the patient actively chose to stop his participation in the study, the patient did not receive any more questionnaires. The participation in the study was then considered to be completed. All data were stored in an Oracle database. The indication and reported ADRs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) on a Lower Level Term, by a qualified assessor. Study drug and co-medication were coded using the Dutch drug dictionary, Z-index.[15] If a report was reported as serious according to the CIOMS criteria, and also assessed as serious by the assessor, a copy of the report was exported to the national database containing all spontaneous reports, where it was handled according to the regulations regarding serious ADR reports. See figure 1 for a schematic description of the workflow.

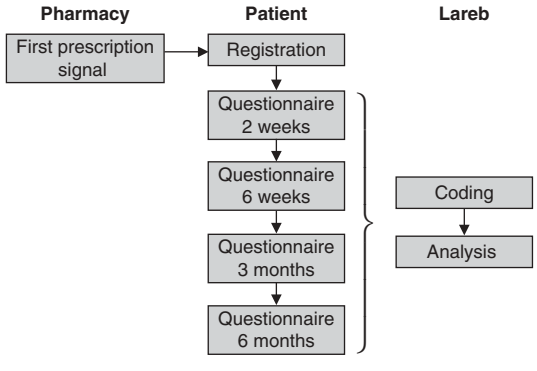

Fig. 1. Flow diagram for Lareb Intensive Monitoring.

Analysis

Descriptive analysis was performed on patient characteristics, drug use and indication for use. The number of patients reporting a possible ADR, the percentage of serious ADRs and the incidence of different ADRs were calculated. Even though a patient could report the same ADRs in all four questionnaires, one specific reaction was only counted once for each individual when calculating incidences. The possible ADRs were divided into labelled or not labelled according to the European Public Assessment Report.[5] Reactions that were not labelled and reactions that were labelled but for other reasons were considered to be of potential interest (selection was undertaken by one pharmacist [LH] and one general practitioner [EvP]) were analysed on a case-by-case basis. Labelled reactions were considered to be of interest if differences were found between the cohort and the Summary of Product Characteristics (SPC). Reactions with serious complications, even though they were labelled, were further analysed.

In the case-by-case analysis, causality was assessed by looking at the temporal relationship between the drug and the reaction, and to exclude other causes for the reaction (for example confounding by indication, concomitant medication). Only reactions where the causality was assessed as at least possible were included.

A comparison between patients who only filled in the registration form and patients who provided data on whether or not they had experienced any possible ADRs was made on the basis of age, sex and daily dosage. Age and daily doses were tested with a t-test, sex was tested with a chi-squared test and significance was declared at the $p < 0.05$ α level.

Data were retrieved using Microsoft Access®. Statistical analysis was performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA).

Results

Between 1 August 2006 and 31 January 2008, 1373 patients registered for the pregabalin study. 796 (58.0%) of these were female. The average age was 54.5 (SD 13) years, ranging from 11–89 years.

Table I. Top six indications for pregabalin use

Indication	No. of patients
Neuropathic pain	1179[a]
Pain	22
Fibromyalgia	20
Epilepsy	11
Back pain	11
Headache	8

a Including indications specifically reported as herpes zoster, complex regional pain syndrome, trigeminal neuralgia and peripheral neuropathy.

Neuropathic pain was the indication in 85.9% of cases. For an overview of reported indications see table I. Pregabalin capsule 75 mg was used by 80.5% of the population cohort, 150 mg was used by 17.0%, 300 mg by 1.2% and the capsule strength used was not specified in 1.8%. The average daily dose was 201 mg. Of all included patients, 1051 (76.5%) filled in at least one questionnaire, providing data on whether or not they had experienced any possible ADRs. For an overview of the response rate see figure 2. There were no statistical significant differences found regarding sex, age and daily dosage between patients filling in a questionnaire compared with patients who only registered for the study.

At least one possible ADR was reported by 728 (69.3%) patients. The reported ADRs, in absolute number, as well as percentages, are presented in table II. Serious ADRs were reported by 11 patients (1.0%). One ADR was categorized as disabling, three as life-threatening, two required hospitalization and five were categorized as 'other'. For an overview of these reactions see table III. Of the patients reporting an ADR, 401 (55.1%) stopped using pregabalin.

Signals

Events not labelled in the SPC and events already labelled but for other reasons were considered to be of interest (e.g. incidence differences) were analysed on a case-by-case basis.

Headache

Headache was reported 43 times during the study, giving an overall incidence of 4.1%. Sixteen of the reports concerned men and 27 concerned women. In all patients the indication was neuropathic pain or other pain-related symptoms (in one case it was for trigeminal neuralgia, which might be a confounding factor). No patients used pregabalin to treat headache or fibromyalgia. Median time to onset was 2 days, ranging from a few hours to 5 months. In 15 reports the headache resolved without stopping the drug and in 16 reports the drug was discontinued due to the headache. In ten reports the headache disappeared after drug discontinuation.

Upper Abdominal Pain

Upper abdominal pain was reported ten times, giving an overall incidence of 1.0%. The reports concerned six women and four men. All patients used pregabalin for neuropathic pain and other pain-related symptoms. Two types of latencies were reported. In four cases the abdominal pain manifested itself immediately (latency <1 week)

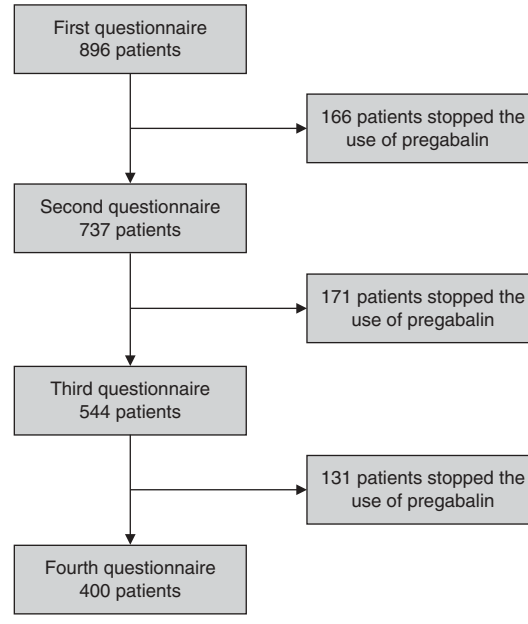

Fig. 2. Response rate per questionnaire. Since patients were allowed to fill in a questionnaire even if they had not completed the previous one, the number of collected questionnaires can exceed the number of the patients filling in the previous questionnaire minus the patients who were reported to have stopped the use of pregabalin in that questionnaire.

Table II. Reported adverse drug reactions (ADRs) that occurred in more than ten patients

ADR	No. of patients (%)
Dizziness	265 (25.2)
Somnolence	146 (13.9)
Feeling drunk	72 (6.9)
Fatigue	68 (6.5)
Weight increased	57 (5.4)
Constipation	47 (4.5)
Headache	43 (4.1)
Dry mouth	43 (4.1)
Disturbance in attention	41 (3.9)
Memory impairment	33 (3.1)
Feeling abnormal	32 (3.0)
Nausea	32 (3.0)
Vision blurred	21 (2.1)
Increased appetite	20 (1.9)
Balance disorder	17 (1.6)
Libido decreased	17 (1.6)
Aphasia	16 (1.5)
Oedema	15 (1.4)
Oedema peripheral	13 (1.2)
Confusional state	12 (1.1)
Palpitations	11 (1.0)
Insomnia	10 (1.0)
Abdominal pain upper	10 (1.0)
Paraesthesia	10 (1.0)

after the start of pregabalin. In these cases the abdominal pain disappeared after cessation of the drug. The other latency was longer, 3–10 weeks. In this group there is no clear temporal relationship between drug use and the reaction. A positive dechallenge was reported in only two of these cases.

Drug Interaction

A possible drug interaction was reported four times during the study. Two of these reports concerned a reaction between pregabalin and blood glucose-lowering agents. In total, 83 patients reported an oral antidiabetic drug or insulin as concomitant medication.

A female aged 62 years used pregabalin 150 mg once daily for neuropathic pain. Concomitant medication was glimepiride (dose not specified), which had been used for more than 5 years. The patient reported an increased effect of glimepiride on the same day as pregabalin treatment was started. The patient recovered after pregabalin withdrawal.

The second report concerned a male patient aged 56 years. He used pregabalin 150 mg twice daily for neuropathic pain. Concomitant medications were diclofenac, oxycodone, enalapril/hydrochlorothiazide, atorvastatin, glimepiride, metformin, insulin aspart and insulin detemir. Four days after initiation of pregabalin treatment the patient experienced hypoglycaemia (glucose levels not provided), which led to an adjustment of his insulin dose. Pregabalin was not withdrawn and the patient recovered because of adjustment of his insulin dose.

Suicidal Ideation

Two separate patients reported suicidal ideation in their reports. The first report concerned a male aged 46 years. He used pregabalin 75 mg twice daily for the treatment of neuropathic pain. Concomitant medication was morphine. Five days after initiation of pregabalin treatment the patient reported that he experienced suicidal ideation. Two weeks thereafter, pregabalin was withdrawn and the patient was reported to be recovering.

The second report concerned a female aged 62 years who used pregabalin 75 mg for neuropathic pain. No concomitant medication was used. Two weeks after initiation of pregabalin treatment and 2 days after withdrawal of the drug the patient reported suicidal tendency. At the time at which the questionnaire was completed, the patient had not recovered from the suicidal tendency.

Discussion

The results of this web-based intensive monitoring study give an overview of not only the safety profile of the drug in daily practice but also capture the characteristics of its users.

Use of Pregabalin in Daily Practice

In this study, the majority of participants (58.0%) were female, which is consistent with the fact that neuropathic pain is more prevalent in females.[3] Age ranged from 11 to 89 years, with

Table III. An overview of serious adverse drug reactions (ADRs)

Sex, age (y)	Category[a]	Suspected ADR	Concomitant medication	Time to onset, action taken and outcome	Comment
F, 58	Other	Somnolence, peripheral oedema, feeling drunk, dyspnoea, hoarseness	Fentanyl, bisoprolol, citalopram, irbesartan, paracetamol (acetaminophen), diazepam,	2 weeks (hoarseness 6 weeks), dose not changed, not recovered	
F, 33	Other	Fall, somnolence, syncope, feeling drunk	Nicomorphine, venlaflaxine, dalteparin, levothyroxine, temazepam, diazepam, omeprazole, naproxen, loperamide, fentanyl, celecoxib	Unknown, drug withdrawn, patient recovered	
F, 63	Life-threatening	Alopecia, CVA	Prednisolone eye drops	Alopecia 1 week, CVA 2 months, drug withdrawn, alopecia outcome unknown, CVA left-sided paralysis	Alopecia was confined to areas with herpes zoster; reporter unsure about relation between CVA and pregabalin since the patient also had hypertension
F, 65	Hospitalization	Balance disorder, memory impairment, upper abdominal pain, anorexia	Isosorbide-5-mononitrate, ranitidine, ursodeoxycholic acid, sucralphate, amoxicillin/clavulanic acid, verapamil, esomeprazole	Memory impairment and balance disorder 4 days, upper abdominal pain and anorexia 2.5 months, drug withdrawn, not recovered	
F, 21	Life-threatening	Increased blood pressure (192/121 mmHg), increased heart rate (145 at rest)	Paracetamol/tramadol	15 days, drug withdrawn, not recovered	Normal blood pressure 130/90 mmHg
F, 40	Hospitalization	Decreased alertness, impaired memory, tongue swelling, fatigue, dizziness	Clonazepam, perindopril, diclofenac, paracetamol, levothyroxine, omeprazole	All events occurred days before the start of pregabalin, drug was withdrawn, not recovered from fatigue and memory impairment, is recovering from all other events	Causality is doubtful in this report
F, 62	Life-threatening	Suicidal tendency	None reported	15 days, drug withdrawn, not recovered	This case is also described in the results section for 'Signals'
M, 47	Disabling	Somnolence, forgetfulness	Citalopram, esomeprazole, etoricoxib, dimethylsulfoxide, ginkgo biloba extract, tramadol, atenolol	5 days for somnolence, 5 months for forgetfulness, dose not changed, not recovered	
F, 58	Other	Numbness, peripheral oedema, increased appetite, fracture in the foot, hyperactivity	None reported	Peripheral oedema, numbness and fracture 4 months, increased appetite and hyperactivity 5 months, dose not changed, not recovered	
F, 43	Other	Weight increase, dizziness, speech disorder, concentration impairment, confusion	Diclofenac	3 months, dose not changed, not recovered	Symptoms prohibited the patient from driving and working
F, 44	Other	Feeling drunk, concentration impairment, balance difficulty, dizziness	Rizatriptan	Hours, dose reduced, recovered	Symptoms prohibited the patient from driving and working

a Seriousness of the reaction according to criteria that include (prolongation of) hospitalization, life-threatening events, reactions leading to death, disabling events, congenital abnormalities and other medically important conditions (those situations in which expedited reporting is deemed appropriate).

CVA = cerebrovascular accident; **F** = female; **M** = male.

four patients in total being younger than 18 years of age. Pregabalin is licensed for patients aged 18 years and over,[5] thus showing that pregabalin, although a relatively new drug, is prescribed off-label to younger patients.

The majority of patients started with the 75 mg capsule, which is in line with the recommended starting dosage (150 mg daily). This dosage can be titrated to 300 mg daily in the first week. It is remarkable that 17 patients started with the 300 mg capsule, which exceeds the recommended starting dose. In this study, pregabalin was used mostly as a treatment for neuropathic pain and only a minority of people used the drug as an antiepileptic. This is probably due to the fact that there are few treatment options for neuropathic pain, whereas there are many effective drugs on the market for the treatment of epilepsy. Another possibility is that the prevalence of neuropathic pain is higher than the prevalence of epilepsy. Some indications reported are types of pain that do not necessarily fall under the term neuropathic pain. It seems that pregabalin is used as a medication for pain that does not respond to treatment with conventional analgesics such as NSAIDs and opioids.

Adverse Drug Reactions

In the Prescription Event Monitoring and the Intensive Medicines Monitoring Programme methodology[16,17] the reported information is treated as adverse events. Although a causality assessment has not been performed on all the information gathered, we have chosen to use the term ADR for the reactions reported because patients are asked only to report symptoms that they believe are associated with the use of pregabalin.

The ADRs most frequently reported in this study correspond to the most frequently reported ADRs in pre-registration trials,[5] as well as in other trials.[18,19] Of the possible ADRs reported via the web-based intensive monitoring system, four are worth additional attention.

Headache is mentioned as an ADR in the SPC of pregabalin, with an unknown frequency. The incidence of headache in this LIM study was 4.1%, indicating that headache might be a commonly occurring ADR. In a study where the efficacy of pregabalin in the treatment of generalized anxiety disorder was investigated, headache occurred in 13.5% of participants in an open-label phase; in the double-blind phase of the study the incidence of headache did not differ between the pregabalin and placebo groups.[19] Results from our study show that latency seems to be short and in some cases the headache resolves without withdrawing the drug; however, in other cases recovery was seen only after drug discontinuation.

Abdominal pain is not mentioned in the SPC of pregabalin. During this study, ten reports were received describing this association. In four of the ten reports, latency was short (<1 week) and a positive dechallenge was reported.

In this study, there were two reports of suicidal ideation. Antiepileptic drugs have been associated with suicidal behaviour and ideation. A meta-analysis performed by the US FDA shows that the use of antiepileptic drugs increases the risk of suicidal behaviour or ideation (odds ratio 1.8; 95% CI 1.24, 2.66). The risk is greater in patients with epilepsy than in patients using these drugs for other indications.[20] This possible ADR should be closely monitored, in particular since its primary use seems to be for pain-related symptoms instead of epilepsy, which is the main indication for other antiepileptic drugs.

In the SPC of pregabalin, hypoglycaemia is mentioned as a rare ADR to pregabalin; however, a possible interaction between pregabalin and blood glucose-lowering drugs is not mentioned.[5] In this study, two reports were found in which hypoglycaemia occurred when pregabalin was added to an already existing treatment with glucose-lowering drugs. In a meta-analysis including 1510 patients in which the efficacy of pregabalin in the treatment of painful neuropathic peripheral neuropathy was investigated, this possible interaction was not found.[18] A literature search via PubMed did not yield any further information concerning a possible interaction between pregabalin and oral blood glucose-lowering drugs. This association is worth further investigation, as our study indicates that the main indication for pregabalin use is neuropathic pain. One can assume that in some of these users neuropathic pain has been caused by diabetes mellitus.

Since patients with diabetic neuropathy might be prescribed pregabalin, it is important to investigate if pregabalin interacts with blood glucose-lowering drugs in order to prevent hypoglycaemia.

Strengths and Weaknesses

Web-based intensive monitoring is an observational prospective cohort study. All patients prescribed pregabalin can be included in the study; there are no limiting inclusion or exclusion criteria compared with clinical trials. A web-based intensive monitoring system will therefore give a picture of the use of pregabalin and its ADRs as it is in daily practice.

The Pharmacy

Eligible patients are identified in the community pharmacy, making it possible to monitor pregabalin prescribed by both general practitioners and specialist doctors in outpatient settings. In the Netherlands, pharmacists play an important role in pharmacovigilance.[21] Fifty percent of all Dutch pharmacies are participating in LIM, however not all of them are active participants. With this number it is assumed that patients going to these pharmacies are a representative sample of the Dutch population. Data on pregabalin prescription during the inclusion period were provided by the Dutch Foundation for Pharmaceutical Statistics.[22] During the inclusion period there were 41 744 first prescriptions of pregabalin in all Dutch pharmacies. Assuming that half of these first prescriptions were filled in a LIM participating pharmacy, approximately 6.6% of the patients given a first pregablin prescription in this time period chose to participate in LIM. Since we have no information about the patients who did not participate, it is not possible to know if the patients eventually participating in the study are representative of all patients using pregabalin. This is a matter that has to be addressed in further research.

The Patient

The role of the patient in pharmacovigilance has been strengthened in recent years, and using patients as a source of information in spontaneous reporting has proven to be successful.[23,24] In this study it was chosen to use the patient as a source of information. This has the advantage that ADRs are reported by the person who has actually experienced the reaction.

In the study, patients were asked to report reactions that they believed were caused by the drug. Thus, it is possible that patients did not report reactions that they did not believe to be attributed to the drug. However, patients do not have any 'professional filter' in what they report, compared with health professionals, therefore underreporting would be less of a problem with patients as reporters. A much given criticism on using patients as a source of information is that it is not medically confirmed and that it can sometimes be difficult to interpret the symptoms reported. However, it is always possible to ask the patient's permission to contact his/her general practitioner for further information.

By using the patient as the source of information, it is possible that people who are retired, or for other reasons are not pursuing a professional career, are more willing to participate in the study because they have more spare time. Because the system is web-based, patients who do not have access to the Internet or are not familiar with using the Internet will be underrepresented in the sample; this would probably be more prominent in the older age categories. Statistics from 2008 show that 86% of Dutch households have access to the Internet at home.[25] It is difficult to draw conclusions to what extent age contributes to the selection bias but because the population using pregabalin has an average age of 54.5 years, one can assume that the impact of older people not being familiar with the Internet would be greater than the number of people having little time to participate in research. It is to be expected that in forthcoming years the elderly will increasingly use the Internet and that this bias will be less important.

Another factor possibly influencing the willingness for a patient to participate in a study investigating ADRs can be their experiences of ADRs in the past. If a patient has experienced an ADR in the past that had implications for their well-being, they might be more prone to participate

in this study. However, susceptibility to ADRs in the past might be a predictor of susceptibility to ADRs in the future. The data collected could therefore give too high an incidence of ADRs because there are more people prone to ADRs participating in the study.

Of the 1373 patients registering for the study, 1051 filled in at least one questionnaire. Of these patients, 69.3% reported an ADR. This number is quite high and it is possible that patients who did experience an ADR are more inclined to fill in a questionnaire compared with those not experiencing any ADRs. Because the patient themself is the source of information, patients with severe illness will be underrepresented because they are not able to fill in the questionnaires themselves.

Conclusions

This study indicates that pregabalin is a relatively safe drug, as used by patients in daily practice over a period of 6 months. It is important when interpreting these results to bear in mind that these data were gathered using information from only a small proportion of patients using this drug during their first 6 months of use.

Eleven patients (<1.0%) out of the total population experienced a serious ADR. Only two patients were hospitalized because of their serious ADR. The most frequently reported reactions in LIM correspond to the reactions that were most frequently reported during clinical trials.

Our study demonstrated that with a web-based intensive monitoring system it is possible to gather information that can contribute to greater knowledge about the characteristic of the reported reactions, allowing for an estimation of the incidence and information about latencies and time course of the reaction, as was the case with headache. It also has the ability to identify new signals, such as abdominal pain and possible interaction with oral antidiabetics.

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References

1. Jensen TS, Gottrup H, Sindrup SH, et al. The clinical picture of neuropathic pain. Eur J Pharmacol 2001 Oct 19; 429 (1-3): 1-11
2. Attal N, Cruccu G, Haanpaa M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol 2006 Nov; 13 (11): 1153-69
3. Dieleman JP, Kerklaan J, Huygen FJ, et al. Incidence rates and treatment of neuropathic pain conditions in the general population. Pain 2008 Jul 31; 137 (3): 681-8
4. Collins SL, Moore RA, McQuay HJ, et al. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. J Pain Symptom Manage 2000 Dec; 20 (6): 449-58
5. Committee for Medicinal Products for Human Use (CHMP). EPAR: Lyrica® [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000546/WC500046602.pdf [Accessed 2010 Dec 1]
6. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res 2007 Feb; 73 (2): 137-50
7. Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ 2004 Jul 3; 329 (7456): 44-7
8. Härmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. Eur J Clin Pharmacol 2008 Aug; 64 (8): 743-52
9. Raine JM. Risk management: a European regulatory view. In: Mann R, Andrews E, editors. Pharmacovigilance. Chichester: John Wiley & Sons Ltd, 2007: 553-8
10. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006; 29 (5): 385-96
11. Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003 Jan; 12 (1): 17-29
12. Härmark L, Kabel JS, van Puijenbroek EP, et al. Web-based intensive monitoring, a new patient based tool for early signal detection [abstract no. 184]. Drug Saf 2006; 29 (10): 1005
13. Oosterhuis I, Härmark L, van Puijenbroek EP, et al. Lareb Intensive Monitoring: an interim analysis [abstract no. P091]. Drug Saf 2007; 30 (10): 960
14. van Grootheest AC, Härmark L, Oosterhuis I, et al. Lareb Intensive Monitoring, a web based system for monitoring ADRs in the postmarketing phase [abstract]. Pharmacoepidemiol Drug Saf 2007; 16: S252-3
15. Z-Index [online]. Available from URL: http://www.z-index.nl [Accessed 2010 Nov 15]
16. Shakir SAW. PEM in the UK. In: Mann R, Andrews E, editors. Pharmacovigilance. Chichester: John Wiley & Sons Ltd, 2007: 307-16
17. Coulter DM. The New Zealand Intensive Medicines Monitoring Programme. Pharmacoepidemiol Drug Saf 1998 Mar; 7 (2): 79-90
18. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized,

controlled trials across a range of doses. Diabetes Care 2008 Jul; 31 (7): 1448-54

19. Feltner D, Wittchen HU, Kavoussi R, et al. Long-term efficacy of pregabalin in generalized anxiety disorder. Int Clin Psychopharmacol 2008 Jan; 23 (1): 18-28
20. Food and Drug Administration. Statistical review and evaluation: anti-epileptic drugs and suicidality [online]. Available from URL: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM192556.pdf [Accessed 2010 Feb 22]
21. van Grootheest AC, van Puijenbroek EP, de Jong-van den Berg LT. Contribution of pharmacists to the reporting of adverse drug reactions. Pharmacoepidemiol Drug Saf 2002; 11 (3): 205-10
22. Dutch Foundation for Pharmaceutical Statistics [online]. Available from URL: http://www.sfk.nl [Accessed 2010 Oct 27]
23. de Langen J, van Hunsel F, Passier A, et al. Adverse drug reaction reporting by patients in the Netherlands: three years of experience. Drug Saf 2008; 31 (6): 515-24
24. van Grootheest K, de Graaf L, de Jong-van den Berg L. Consumer adverse drug reaction reporting: a new step in pharmacovigilance? Drug Saf 2003; 26 (4): 211-7
25. Centraal Bureau voor de Statistiek. Mediaproducten steeds meer via internet [media release]. 2008 Oct 28 [online]. Available from URL: http://www.cbs.nl/nl-NL/menu/themas/vrije-tijd-cultuur/publicaties/artikelen/archief/2008/2008-071-pb.htm [Accessed 2010 Oct 27]

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