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ORIGINAL REPORT

Longitudinal monitoring of the safety of drugs by using a web-based system: the case of pregabalin†

Linda Härmark[1,2]*, Eugene van Puijenbroek[1] and Kees van Grootheest[1,2]

[1]*Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands*
[2]*Department of Pharmacy: Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, The Netherlands*

ABSTRACT

Purpose Information about the time course of adverse drug reactions (ADRs) is often lacking. If this information would be available, it could help increase patient's adherence to drugs when experiencing an ADR. The aim of this study was to demonstrate how a web-based intensive monitoring system using the patient as a source of information can be used to gather longitudinal safety data of a drug. In this study, pregabalin was used as an example.

Methods First-time users of pregabalin were approached in Dutch pharmacies between 1 August 2006 and 31 January 2008. After online registration, patients received questionnaires by email 2 weeks, 6 weeks, 3 months and 6 months after the start of the drug use. Data on patient characteristics, drug use and ADRs were collected and analysed.

Results A total of 1373 patients registered for the pregabalin study. Of these patients, 1051 (76.5%) filled in at least one questionnaire. On an aggregated level, the ADR profile remained relatively stable over time. Incidence densities showed that the five most frequently reported reactions occurred early in the treatment. Initially, the majority of the patients did not undertake any action when experiencing an ADR. Recovery did not seem to be completely dependent of drug cessation.

Conclusions With web-based intensive monitoring, it is possible to study the time course of ADRs. This method can be a valuable addition to pharmacovigilance because it can generate other types of information as compared with spontaneous reporting and other intensive monitoring methodologies. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—pharmacovigilance; intensive monitoring; longitudinal data collection; pregabalin

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INTRODUCTION

For a pharmacological intervention to be successful, the right drug has to be prescribed for the right condition in the right patient. However, these criteria are not the only things necessary to ensure that a patient benefits from the drug. Patient adherence, the extent to which patients take medications as prescribed by their healthcare provider, is essential to achieve the intended effect.[1] Studies have shown that the occurrence of adverse drug reactions (ADRs) or the fear thereof is of great importance when it comes to a patient's adherence.[2–4] To increase adherence, it is important to have access to information about ADRs. Information about time to onset of the ADR, how long it persists and if it disappears spontaneously or not can help to motivate the patient to be adherent to their medication when experiencing an ADR.

Traditionally, medical doctors and in some countries also pharmacists have been the main source of information in pharmacovigilance.[5] In a spontaneous reporting system, doctors and pharmacists provide mainly cross-sectional information about the ADR, that is, the status of the ADR at the time of reporting. In a few cases, follow-up information is provided, but this is not the case in all reports because reporting as well as providing follow-up information is a time-consuming task for the healthcare professional. Spontaneous reporting was not developed to gather the information mentioned previously and is therefore not able to capture it. To fill this gap, new methods need to be developed.

In recent years, the patient is getting more involved in drug safety. A number of countries around the world

*Correspondence to: L. Härmark, Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's-Hertogenbosch, The Netherlands.
E-mail: l.harmark@lareb.nl
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have introduced patient reporting to their spontaneous reporting systems, and the experiences so far are favourable.[6,7] The new European pharmacovigilance legislation underpins the role of consumer reporting by making it mandatory. As patient involvement increases drug safety, patients become an important new source of information about the safety of a drug.

In the Netherlands, the Netherlands Pharmacovigilance Centre Lareb has been responsible for the collection and analysis of spontaneous reports since 1995. In 2006, a web-based intensive monitoring system, called Lareb Intensive Monitoring (LIM), was introduced as a complement to the spontaneous reporting system. Intensive monitoring is a non-interventional observational cohort, which can monitor selected drugs over time. The Intensive Medicines Monitoring Programme in New Zealand[8] and the Prescription Event Monitoring in the UK[9] are examples of intensive monitoring programmes. Although the methodology of LIM has similarities with these programmes, it has characteristics that distinguish it from them. The main differences are that the source of information is not the health professional but the patient, data are collected at several points in time and the system is web-based. The longitudinal character of data collection makes it possible to study the time course of ADRs.

The aim of this study was to demonstrate how a web-based intensive monitoring system using the patient as a source of information can be used to gather longitudinal safety data of a drug. In this study, pregabalin (Lyrica®, Pfizer, New York, NY) was used as an example.

Pregabalin is a relatively new drug registered for the treatment of neuropathic pain, as adjuvant therapy in the treatment of epilepsy and for generalised anxiety disorder.[10] It is a gamma-aminobutyric acid analogue and exerts its effects by binding to the α_2–δ subunit of voltage-gated calcium channels, leading to a decreased synaptic release of neurotransmitters.[11]

METHOD

Lareb Intensive Monitoring identifies first-time users of a drug in a pharmacy by using the first prescription signal. The first prescription signal is generated if the patient has not filled in a prescription of that particular drug in the previous 12 months, based on the information from that particular pharmacy. Patients in the Netherlands are linked to one pharmacy only, which makes it is possible to monitor a patient's drug use. Eligible patients are asked to participate in the study. After online registration, the patient is sent periodic questionnaires per email, in which information about drug use and possible ADRs is collected. If the patient has not experienced any ADRs, this will be reported as well.[12–14] The LIM methodology has been described in more detail elsewhere.[15]

Study population

First-time users of pregabalin were approached in Dutch pharmacies between 1 August 2006 and 31 January 2008. Data were collected between 1 August 2006 and 31 July 2008.

Data collection

Patient characteristics such as gender, birth date, length and weight were asked for. Information about pregabalin use including start date, strength, product code, dosage, administration form and indication was collected. This information was also gathered for all concomitant medication. For a detailed overview of the questionnaires, see Härmark *et al.*[15] After registration, the patient received questionnaires by email 2 weeks, 6 weeks, 3 months and 6 months after the start of the drug use. In these questionnaires, questions about possible ADRs, which were considered to be related to the use of pregabalin, were asked. Furthermore, the seriousness of the reaction according to the Council for International Organisations of Medical Sciences criteria[16], the start date of the reaction, the action taken after experiencing an ADR, the action taken with pregabalin (stopping/dose reduction/no dose change) and the outcome of the reaction were asked for. If the patient did not fill in the questionnaire immediately, a reminder was sent 5 days later. If a questionnaire was not completed, the patient was considered 'lost to follow-up' for the questionnaire.

If the patient stopped the use of pregabalin, reasons for stopping were asked. In the event of death of the patient or if the patient actively chose to stop his or her participation in the study, the patient did not receive any more questionnaires. The participation in the study was then considered to be completed on the date the notification was received. Indication and reported ADRs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Indication and ADRs were coded on a lower-level term level by a qualified assessor.[17] Study drug and co-medication were coded using the Dutch drug dictionary.[18] If a report was considered to be serious according to the Council for International Organisations of Medical Sciences criteria, a copy of the report was forwarded to the national database containing all spontaneous reports, where it was handled according to the regulations regarding serious ADR reports.[19]

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Analysis

Cohort characteristics. Descriptive analysis was performed on the response rate, age, gender, indication for use and daily doses.

Adverse drug reaction spectrum of pregabalin at different points in time. The number of patients reporting and ADRs were grouped per questionnaire and per MedDRA system organ class (SOC).

Reactions belonging to the SOC nervous system disorders were, in addition, grouped per questionnaire and per MedDRA preferred term (PT).

The absolute number of ADRs per SOC or per PT per questionnaire was divided by the total number of patients who responded to the questionnaire in order to calculate the percentage of patients experiencing the ADR at that specific point in time.

Additional information on the top five reported adverse drug reactions. Incidence densities were calculated for the five most frequently reported ADRs during four different periods (0–2 weeks, 2–6 weeks, 6–12 weeks and 12–26 weeks). If a patient reported more than one reaction falling into this PT, the latency for the first reaction was used. If the patient did not provide a date on which he or she stopped using pregabalin, it was assumed that the patient stayed in the cohort for as long as he or she kept filling in the questionnaires. The time to onset of the reactions was graphically illustrated as Kaplan–Meier curves.

Descriptive analysis was undertaken on the action taken with the drug when experiencing an ADR, and the outcome of the reaction. In the analysis of the outcome of the reaction, the total number of answers exceeded the number of patients because one or more answers could be chosen.

All data were retrieved using MS Access. Statistical analysis was performed using SPSS 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

Cohort characteristics

A total of 1373 patients registered for the pregabalin study, and 796 (58.0%) of these patients were women. The average age was 54.5 years (standard deviation = 13), ranging from 11 to 89 years. Neuropathic pain was the indication in 85.9% of the cases. The average daily dosage was 201 mg. Of these patients, 1051 (76.5%) filled in at least one questionnaire, 896 filled in the first questionnaire and 737, 544 and 400 filled in the remaining questionnaires.

Adverse drug reaction spectrum of pregabalin at different points in time. In total, 1503 possible adverse drug reactions were reported by 728 patients. Of these patients, 534 reported their first ADR in the first questionnaire, 134 in the second questionnaire, 39 in the third questionnaire and 21 in the last questionnaire.

Reactions belonging to the SOC nervous system disorders are the most frequently reported. Figure 1 shows the whole ADR profile for pregabalin per MedDRA SOC. Figure 2 shows the ADR profile for ADRs belonging to the SOC nervous system disorders per MedDRA PT.

The five most frequently reported ADRs, namely, dizziness, somnolence, feeling drunk, fatigue and weight increase were analysed in more detail. Table 1 shows the incidence density of dizziness. Figure 3 shows the corresponding Kaplan–Meier curve. Table 2 shows the action taken with the drug when experiencing an ADR and the outcome of the ADR when stopping and continuing pregabalin use.

DISCUSSION

In pharmacovigilance, there is a need for more information about ADRs. Information about when the ADR occurs, how long it persists and if it disappears spontaneously or not can help to motivate the patient to be adherent to their medication when experiencing an ADR. In this article, we illustrate that a web-based intensive monitoring system using the patient as a source of information can be used to generate this type of information.

The results from the pregabalin study will be discussed first and thereafter the role of web-based intensive monitoring as a new pharmacovigilance tool.

The adverse drug reaction profile of pregabalin

Calculation of incidence densities and Kaplan–Meier curves show that the five most frequently reported reactions occur early in the treatment, with the highest incidence in the first 2 weeks. This is consistent with the fact that these ADRs are probably type-A ADRs, a direct pharmacological effect of the drug.[20]

It is surprising that after the first 2 weeks the ADR profile on an aggregated level did not change. It is believed that ADRs, which can be attributed to the pharmacological properties of the drugs, would be more pronounced in the beginning of the treatment and would disappear spontaneously if drug treatment continued. This does not seem to apply in all cases. Another reason that the ADR profile did not change (less ADRs) over time is that patients probably continue their drug use

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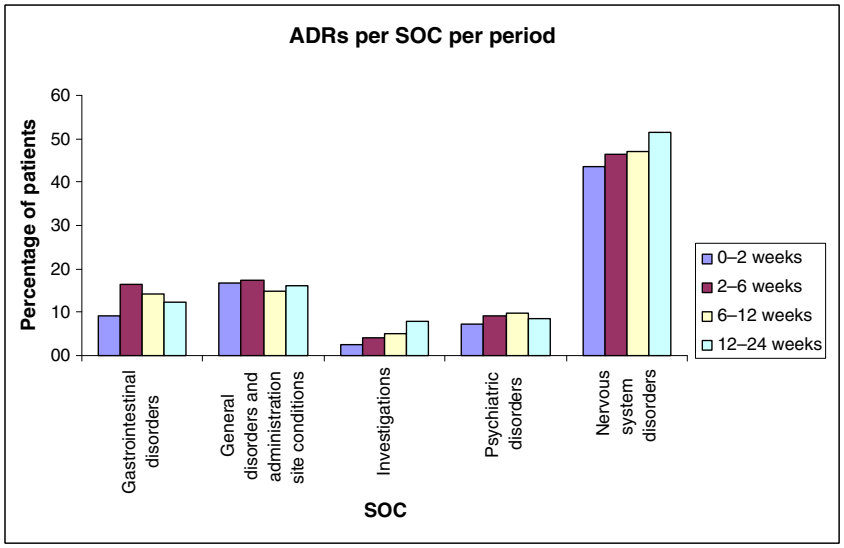

Figure 1. Percentage of patients experiencing an adverse drug reaction because of pregabalin use during different periods. Adverse drug reactions were grouped per system organ class. The five system organ classes with the most reported adverse drug reactions are shown. ADRs, adverse drug reactions; SOC, system organ class

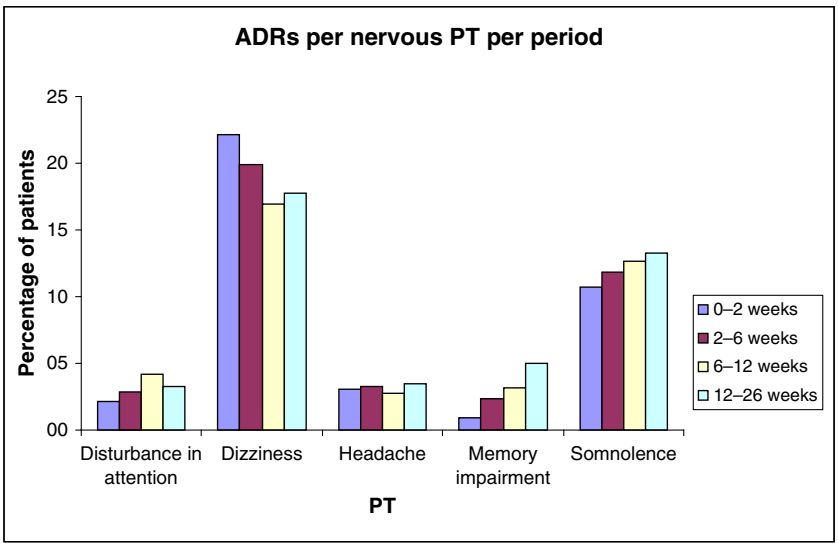

Figure 2. Percentage of patients experiencing an adverse drug reaction belonging to the SOC nervous system disorders. Adverse drug reactions were grouped per preferred term. The five preferred terms with the most reported adverse drug reactions are shown. ADRs, adverse drug reactions; PT, preferred term

Table 1. Incidence densities per 1000 person-days per period for the five most frequently reported adverse drug reactions associated with pregabalin use

	0–14 days	15–42 days	43–90 days	91–180 days
Dizziness	18.0	1.0	0.34	0.05
Somnolence	7.4	0.53	0.10	0.17
Feeling drunk	4.0	0.32	NA	NA
Fatigue	3.9	0.16	0.09	NA
Weight increase	1.6	0.38	0.13	0.11

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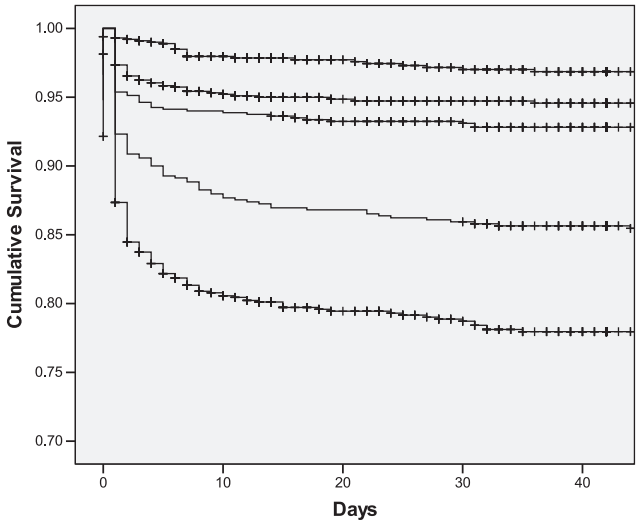

Figure 3. Kaplain–Meier curves illustrating the incidence densities of the five most frequently reported adverse drug reactions. From the top down to the first line represents increased weight followed by fatigue, feeling drunk, somnolence and dizziness. 'Survival' pertains to those patients who did not develop particular adverse drug reaction, and '+' represents the censored patients

Table 2. The action taken with the drug after experiencing an adverse drug reaction and the outcome of the reaction depending on whether the drug was withdrawn or not shown in absolute numbers as well as in percentages

	Dizziness	Somnolence	Feeling drunk	Fatigue	Weight increase
Action taken with the drug after experiencing an ADR*					
No action	39 (44.3%)	18 (43.9%)	11 (32.4%)	14 (36.8%)	13 (52.0%)
Dose reduced after consultation	8 (9.1%)	4 (9.8%)	4 (11.8%)	2 (5.3%)	1 (4%)
Drug withdrawn after consultation	19 (21.6%)	3 (7.3%)	8 (23.5%)	8 (21.15%)	6 (24.0%)
Dose reduced on own initiative	6 (6.9%)	3 (7.3%)	4 (11.8%)	3 (7.9%)	0
Drug withdrawn on own initiative	7 (8.0%)	4 (9.8%)	3 (8.9%)	3 (7.9%)	2 (8.0%)
Other reasons	9 (10.2%)	9 (22.0%)	4 (11.8%)	8 (21.1%)	3 (12.0%)
Outcome of the ADR after stopping pregabalin use					
Recovering/resolving	80 (66.1%)	42 (82.4%)	30 (79.0%)	19 (57.6%)	11 (45.8%)
Not recovered	25 (20.7%)	3 (5.9%)	4 (10.5%)	9 (27.2%)	11 (45.8%)
Unknown	16 (13.2%)	6 (11.8%)	4 (10.5%)	5 (15.1%)	2 (8.3%)
Outcome of the ADR while continuing pregabalin use					
Recovering/resolving	67 (46.5%)	40 (41.1%)	14 (41.2%)	12 (34.3%)	4 (12.1%)
Not recovered	76 (52.7%)	55 (57.9%)	20 (58.0%)	22 (62.9%)	29 (87.9%)
Unknown	1 (0.7%)	0	0	1 (2.9%)	0

ADR = adverse drug reaction.
Because not all patients had answered all questions, the number of patients on the different questions was not always constant.
*Because one or more answers could be chosen, the total number of answers exceeded the number of patients.

even when experiencing an ADR. Apparently, the positive effects of the drugs outweigh the negative effects when deciding to continue drug use.

Initially, the majority of the patients did not undertake any action when experiencing an ADR. The differences in the outcome of the reaction between patients who withdrew the drug and patients who continued drug treatment are dependent on the type of ADR. For example, for dizziness, 66.1% of the patients who had stopped pregabalin use were reporting to have recovered or were recovering. In contrast, 46.5% of those who continued pregabalin use reported that they were recovering or had recovered. In this case, a rather large proportion of the patients who continued the use of pregabalin also recovered from dizziness, indicating that dizziness may be a transitory ADR, not always requiring cessation of the drug in order to disappear. For weight increase, drug withdrawal had a more pronounced effect on recovery: 45.2% of the patients recovered after drug cessation compared with 12.1% of those who continued drug use. In this case, it seems that the outcome is more dependent on drug cessation as is the case with dizziness.

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Web-based intensive monitoring

The LIM system was developed as an addition to the spontaneous reporting system. Spontaneous reporting systems are a great source of information when it comes to identifying new signals, especially concerning serious and rare ADRs. Of the major safety issues in recent years, majority were identified using evidence from spontaneous reporting.[21] Spontaneous reporting has a few limitations, for example, underreporting and inability to calculate incidences. In addition, it only provides cross-sectional data of the reaction, which do not provide any information about the time course of the reaction.

With a web-based intensive monitoring system, it is possible to address a few of the limitations of spontaneous reporting. With this system, incidences of certain reactions can be calculated, and because of its longitudinal character, it is also possible to collect information about the time course of ADRs. In the following paragraphs, the strengths and weaknesses of this system will be discussed.

In the literature, most information available about the ADRs of a newly marketed drug originate from randomised controlled trials, where strict inclusion and exclusion criteria are present and where the duration of the trial is usually quite short. With web-based intensive monitoring, there are no inclusion or exclusion criteria that might lead to a different population than in clinical trials, and therefore, it will give a better picture of the ADR profile in daily practice.

Even though there are no restrictions for inclusion in the web-based intensive monitoring system, there might be a 'selection' of the patient population. Only 6.6% of all the patients who received a first prescription of pregabalin decided to participate in the study (data provided by the Dutch Foundation for Pharmaceutical Statistics). Because we have no information about the patients who did not participate, it is not possible to know if the patients who eventually participated in the study are representative for the patients using pregabalin, which means that the results have to be interpreted with this in mind.

For this web-based intensive monitoring to be a powerful tool in generating new data about ADRs, patient participation has to be increased. To in-crease patient participation, there are activities ongoing in order to stimulate active participation from the pharmacist (e.g. pharmaceutical care proj-ects, training) as well as research into the motives for patient participation and investigation of the non-responders.

In this study, we chose 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. Reactions that are not perceived as ADRs or which are asymptomatic will not be reported. In a few SOCs, for example, blood and lymphatic disorders, ear and labyrinth disorders, endocrine disorders, hepatobiliary disorders and immune system disorders, no or very few reports were received. ADRs falling into these categories are of course quite rare, but it is possible that patients do not have tangible symptoms of ADRs concerning these organs or that patients do not correlate these complaints to drug use. If a patient experiences an ADR which unables him to fill in any further questionnaires, this information will not be collected. It is therefore possible that the system will be less valuable in order to detect these types of reactions.

Because all questionnaires are web-based, it is possible to send a patient multiple questionnaires over time. Longitudinal data collection makes it possible to study the time course of ADRs. In a study where multiple questionnaires are sent, there is always a risk of receiving conflicting information. In the questionnaires, there were no logical checks for start dates and end dates; that is, it was not checked for if the start date of the drug proceeded the start date of the ADR, which sometimes hampered calculating, for example, latency times. Another example concerning conflicting information is the outcome of the reaction. The patient was allowed to give the answer that he or she had recovered and had not recovered at the same time. In the analysis, this was addressed by choosing the least favourable outcome (not recovered > recovering > recovered), so there would not be an overestimation of positive outcomes.

During data analysis, it became clear that the patients did not always report the suspected ADRs in the questionnaire, which covered the period in which they experienced the ADR, but they reported it in one of the remaining questionnaires. In the analysis for incidence densities, it is corrected for this, and the latency of the reaction was calculated based on the start date of the drug and the start date of the reaction rather than calculated based on the number of reactions in each questionnaire, thereby assuming that the reaction occurred in the questionnaire in which it was reported.

A weakness with the longitudinal character of this study is that patients were allowed to fill in a questionnaire even though they had not filled in the previous questionnaire. By allowing skipping questionnaires, the chance that patients fill in a questionnaire when experiencing an ADR is greater than when they are not, giving an overestimation of ADRs occurrence. To address this bias, an analysis could

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have been made with the data from the patients who filled in the questionnaires sequentially. In future studies, this will not be a problem because we will change the process of sending of the questionnaires. Only those who fill in a questionnaire will receive the other questionnaires.

Because the system is web based, patients who do not have access to 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 the Dutch households have access to Internet at home.[22] It is difficult to draw conclusions to what extent age contributes to the selection bias, but older people not being familiar with the Internet would be underrepresented in this study.

Because the web-based intensive monitoring methodology is new, there are some refinements necessary as discussed previously. However, this study shows that it is possible to study the time course of ADRs by using a web-based intensive monitoring. This method can be a valuable addition to pharmacovigilance because it can generate other types of information as compared with spontaneous reporting and other intensive monitoring methodologies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- With web-based intensive monitoring, it is possible to study ADRs over time, both on an aggregated and detailed level.
- Web-based intensive monitoring can be a valuable addition to pharmacovigilance because it can generate other types of information as compared with spontaneous reporting and other intensive monitoring methodologies.

REFERENCES

1. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; **353**(5): 487–497.
2. Kwara A, Herold JS, Machan JT, *et al*. Factors associated with failure to complete isoniazid treatment for latent tuberculosis infection in Rhode Island. *Chest* 2008; **133**(4): 862–868.
3. Baldessarini RJ, Perry R, Pike J. Factors associated with treatment nonadherence among US bipolar disorder patients. *Hum Psychopharmacol* 2008; **23**(2): 95–105.
4. Kane SV, Brixner D, Rubin DT, *et al*. The challenge of compliance and persistence: focus on ulcerative colitis. *J Manag Care Pharm* 2008; **14**(1 Suppl A): s2–s12.
5. van Grootheest K, Olsson S, Couper M, *et al*. Pharmacists' role in reporting adverse drug reactions in an international perspective. *Pharmacoepidemiol Drug Saf* 2004; **13**(7): 457–464.
6. 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): 515–524.
7. Aagaard L, Nielsen LH, Hansen EH. Consumer reporting of adverse drug reactions: a retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. *Drug Saf* 2009; **32**(11): 1067–1074.
8. Harrison-Woolrych M, Coulter DM. PEM in New Zealand. In Pharmacovigilance, Mann R, Andrews E (eds). John Wiley and Sons, Ltd: Chichester, 2007; pp. 317–332.
9. Shakir SAW. PEM in the UK. In Pharmacovigilance, Mann R, Andrews E (eds). John Wiley and Sons, Ltd: Chichester, 2007; pp. 307–316.
10. SPC Lyrica®. EMA, London. http://www.emea.europa.eu/humandocs/PDFs/EPAR/lyrica/emea-combined-h546en.pdf [13 August 2009].
11. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel α_2–δ (alpha$_2$–delta) subunit as a target for antiepileptic drug discovery. *Epilepsy Res* 2007; **73**(2): 137–150.
12. Härmark L, Kabel JS, van Puijenbroek EP, *et al*. Web-based intensive monitoring, a new patient based tool for early signal detection. *Drug Saf* 2006; **29**(10): 911–1010.
13. Oosterhuis I, Härmark L, van Puijenbroek EP, *et al*. Lareb Intensive Monitoring: an interim analysis. *Drug Saf* 2007; **30**(10): 919–990.
14. Van Grootheest AC, Härmark L, Oosterhuis I, *et al*. Lareb Intensive Monitoring, a web based system for monitoring ADRs in the postmarketing phase. *Pharmacoepidemiol Drug Saf* 2007; **16**: S252–S253.
15. Härmark L, van Puijenbroek E, Straus S, *et al*. Intensive monitoring of pregabalin: results from an observational, web-based, prospective cohort study in the Netherlands using patients as a source of information. *Drug Saf* 2011; **34**(3): 221–231.
16. Council for International Organisations of Medical Sciences. International Reporting of Adverse Drug Reactions. CIOMS Working Group Report. World Health Organisation: Geneva, 1987.
17. MedDRA and MSSO. http://www.meddramsso.com/MSSOWeb/index.htm [19 August 2010].
18. Z-Index. http://www.z-index.nl/frameset.htm [19 August 2010].
19. The Council of the European Communities. Regulation (EEC) No 2309/93. Version date: 22 July 1993. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_1993_2309/reg_1993_2309_en.pdf [19 August 2010].
20. Meyboom RH, Lindquist M, Egberts AC. An ABC of drug-related problems. *Drug Saf* 2000; **22**(6):415–423.
21. Raine JM. Risk management—a European regulatory view. In Pharmacovigilance, Mann R, Andrews E (eds). John Wiley and Sons, Ltd: Chichester, 2007; pp. 553–558.
22. Centraal Bureau voor de Statistiek. Mediaproducten steeds meer via Internet. Version date: 28 August 2008. http://www.cbs.nl/nl-NL/menu/themas/vrije-tijd-cultuur/publicaties/artikelen/archief/2008/2008-071-pb.htm [29 November 2010].