Eur J Clin Pharmacol (2016) 72:615–622
DOI 10.1007/s00228-016-2019-z

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Time course, outcome and management of adverse drug reactions associated with metformin from patient's perspective: a prospective, observational cohort study in the Netherlands

Loek de Jong[1] · **Linda Härmark**[1] · **Eugène van Puijenbroek**[1,2]

Received: 8 September 2015 / Accepted: 27 January 2016 / Published online: 11 February 2016

Abstract
Purpose The aim of this study was to gather information about frequency, latency time, outcome and management of frequently occurring adverse drug reactions (ADRs) related to the use of metformin in daily practice.
Methods A prospective, observational cohort study was performed. A total of 2490 first-time metformin users were recruited through pharmacies in the Netherlands between February 1, 2008, and April 1, 2012. Patients were invited to complete six web-based questionnaires at 2-week, 6-week, 3-month, 6-month, 9-month and 12-month intervals after starting treatment with metformin. Information was gathered about patient characteristics, ADRs and drug use.
Results The occurrence of at least one possible ADR related to the use of metformin was reported by 34.5 % of the patients. A higher proportion of females reported the occurrence of an ADR (39.6 %) compared to the proportion in males (30.9 %). Some patients (11.4 %) stopped using metformin within 1 year after start. More than half of the patients (50.8 %) undertook no action regarding metformin after the occurrence of ADRs. A high number of patients (77.7 %) recovered or were still recovering from ADRs despite continuation of metformin. Most ADRs occurred shortly after the beginning of the treatment, with a median latency time of 1–6 days. The study revealed some ADR-specific differences in occurrence rate, latency time, management and outcome.
Conclusion This study successfully obtained information about frequency, latency time, outcome and management of frequently occurring ADRs related to the use of metformin in daily practise.

Keywords Diabetes · Survey · ADR · Side effects · Drug safety

Introduction

Metformin was first introduced on the global market in 1959. Despite the availability of several novel blood glucose-lowering agents, metformin remains the cornerstone in the treatment of T2DM, especially in overweight patients. The most common adverse drug reactions (ADRs) of metformin include gastrointestinal symptoms like nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Other less frequent ADRs include dysgeusia, skin reactions, abnormal liver functions, hepatitis and vitamin B_{12} deficiency [1]. A rare, but serious, ADR of metformin is lactic acidosis, with a mortality rate of around 25 % [2]. Although the type and frequency of metformin-related ADRs are well known, little is known about time course, outcome and management of metformin-related ADRs in daily practice. Knowledge of these characteristics of ADRs can help clinicians and patients in adequate prediction and handling of metformin-related ADRs. Among patients with T2DM, it has been shown that poor adherence to diabetic drugs can compromise safety and treatment effectiveness and thereby lead to increased morbidity and mortality [3]. Poor medication adherence is a complex problem with many contributing causes. As shown with other chronic medication, concerns about ADRs can be a common reason for drug

Electronic supplementary material The online version of this article (doi:10.1007/s00228-016-2019-z) contains supplementary material, which is available to authorized users.

✉ Loek de Jong
loekdejong1@gmail.com; l.dejong@lareb.nl

[1] Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, Netherlands

[2] Pharmacotherapy and pharmaceutical care, University of Groningen, Groningen, Netherlands

discontinuation [4]. When patients start a new drug for a chronic condition, it has been shown that intentional nonadherers have lower perceptions of the necessity of their new medication and higher levels of concerns about taking it, compared to adherers [5]. Although insignificant, it has been shown that patients with T2DM who are intentional nonadherers have higher concerns about their drugs, compared to adherers [6]. To improve drug adherence, healthcare providers should effectively address concerns about medication [7, 8]. However, this requires knowledge of frequencies, latency times, outcomes and management of ADRs.

The primary goal of this study is to gather information about frequency, latency time, outcome and management of frequently occurring ADRs related to the use of metformin in daily practice. As secondary goals, we investigated the relationship between genders on the occurrence of ADRs and investigated if the study population was an adequate reflection of all metformin users in the Netherlands.

Method

Web-based intensive monitoring system

The Netherlands Pharmacovigilance Centre Lareb has developed a web-based intensive monitoring system, called Lareb Intensive Monitoring (LIM). LIM follows first-time users of a specific drug during a predefined period of time. Data is collected using web-based questionnaires which are sent automatically to the patient at specific moments. Data obtained with LIM reflects information from the patients' perspective. The LIM methodology has been described in more detail elsewhere [9].

Study population

Although patients are free to fulfil their prescriptions at any pharmacy, the majority of patients in the Netherlands are linked to one pharmacy only. This makes it possible to monitor the drug use of a patient based on these pharmacy data. The study cohort consisted of first-time metformin users, identified through the first prescription signal in one of the intensive monitoring participating pharmacies (approximately 1380) between February 1, 2008, and April 1, 2012. Patients who started metformin more than 2 weeks prior to registration were not able to register for the study.

Questionnaires

During the first drug dispensation of metformin, pharmacies handed out a LIM leaflet to the patient. The leaflet contained an activation code for the study, allowing patients to sign up for the study online. Upon online registration, information was gathered about patient characteristics (gender, date of birth, weight, height, e-mail address and pharmacist), metformin use (start date and indication) and use of concomitant drugs. After registration, patients were included in the study and invited to complete six questionnaires by e-mail at 2-week, 6-week, 3-month, 6-month, 9-months and 12-month intervals after the reported start date of metformin. Patients completed these questionnaires on a voluntary basis. Information was collected about possible metformin-related ADRs. If a patient reported a possible ADR, specific information was gathered about date of onset, management, outcome and seriousness of the reaction according to criteria of the Council for International Organizations of Medical Sciences (CIOMS) Working Party [10]. Patients could also give a short description of the reaction. A patient would receive a reminder if the questionnaire was not completed within 5 days after the first invitation. If the questionnaire was still not completed within 4 weeks after the reminder, the patient was considered as lost to follow-up for that specific questionnaire. However, the patient would still be invited to complete the next questionnaire. If a patient had indicated in a questionnaire to stop further participation, the patient would not receive any more questionnaires.

Data collection

All data was stored in an Oracle database. Reported ADRs and indications were coded by an experienced qualified assessor using the Medical Dictionary for Regulatory Activities (MedDRA) terminology [11]. Metformin and co-medication were coded using the Dutch drug dictionary (Z-index) [12]. Serious reports, according to the CIOMS criteria, were transmitted to the national database and handled in the same way as serious spontaneous reports.

Analysis

Data extraction and analysis were performed using Microsoft® SQL Server® 2012 and Microsoft® Excel® 2013. Descriptive analysis was performed on patient characteristics. To calculate the frequency of each specific ADR, we used the number of patients who had reported a specific ADR within the study period and the total number of patient registrations. Latency time of all reactions reported in ≥1 % of the patients was calculated using the reported start date of metformin vs. the start date of the ADR. If a patient reported the occurrence of the same ADR through different questionnaires, only the first occurrence of the specific ADR was included for analysis. Cases were included if the start date of metformin and the start date of the reaction were fully present (day, month, year). Cases were excluded when the reported start date of the ADR was before the reported start date of metformin.

The number of patients who reported an ADR was determined for every questionnaire, as well as the action taken with the drug after the occurrence of an ADR and the outcome after

the patient had stopped or continued the use of metformin. For the action taken with the drug, the patients were able to choose between seven predetermined actions including the action 'other'. If a patient reported the same action taken with metformin after experiencing an ADR, the specific action was only counted once. If a patient reported different actions throughout different questionnaires, only the action of highest importance was counted ('drug withdrawn after consultation' was considered as most important and 'no action' was considered as least important). The same principle was applied to the outcome of the ADR after withdrawal, where 'recovered after withdrawal' was considered as most important and 'unknown after withdrawal' was considered as least important. For the outcome of an ADR after continuing metformin, 'recovered after continuing' was considered as most important and 'unknown after continuing' was considered as least important.

The response rate for each questionnaire was calculated using the number of patients still using metformin who were invited for the questionnaire and the number of responders. Frequencies of ADRs were also specified according to gender in order to look at gender-specific differences. The study population was compared with general patient information from the Dutch Foundation for Pharmaceutical Statistics (SFK). In the Netherlands, over 95 % of all pharmacies collaborate with the SFK [13]. Using this comparison, it was possible to check if the study population was an adequate reflection of all metformin users in the Netherlands. A Pearson's χ^2 test was used to compare for sex. A p value <0.05 was considered statistically significant.

Results

Patient characteristics

A total number of 2490 patients signed up for the study. An overview of patients' characteristics is shown in Table 1. The proportion of males who signed up for the study (59 %) was higher ($p < 0.001$) than the proportion of males in the SFK data (52 % male). Two children, aged 12 and 15 years old, were included in the study. The oldest person was 89 years old. The average age in the studied population (59.2 years (95 % confidence interval (CI) 58.8–59.6)) differed from the average age from the SFK data concerning first-time users of metformin (60.7 years (95 % CI 60.6–60.8)). At registration, 1846 patients (74 %) reported that they were using one or more concomitant drug. The average number of concomitant drugs was 3.3 (95 % CI 3.2–3.4).

Response rate

A total number of 2089 patients (83.9 %) filled in at least one questionnaire. The response rate per questionnaire is shown in Fig. 1.

ADRs

During the study, 858 patients (34.5 %) reported the occurrence of at least one ADR. A higher proportion of females reported the occurrence of an ADR (39.6 %) compared to the proportion in males (30.9 %). In total, 1584 individual ADRs were reported including 151 unique ADRs. Table 2 shows the frequencies of ADRs that were reported in more than 1 % of the patients. An overview of frequencies of all ADRs that were reported in the study is given in Online Resource 1.

A total of 285 patients (11.4 %) reported that they had stopped the use of metformin within 1 year after start. Even though metformin was more often withdrawn in females (12.6 %) compared to males (10.6 %), no significant difference was found ($p = 0.119$). The most reported reason given for the withdrawal of metformin was the occurrence of ADRs (49.5 % of patients), followed by other unspecified reasons (25.3 % of patients), disappearance of the symptoms (18.2 % of patients), ineffectiveness (9.5 % of patients) and unknown reasons (3.9 %). Because patients were able to report more than one reason for the withdrawal of metformin, the sum of these percentages exceeds 100 %.

We investigated the actions taken with the drug after experiencing an ADR and the outcome of the reaction depending on whether the drug was withdrawn or not. Table 3 gives an overview of these data for the five most frequently reported ADRs and for all ADRs combined. The majority of patients who responded to the question about the action taken with metformin after the occurrence of an ADR undertook no action regarding metformin. Most of the patients consulted their healthcare provider before dose reduction or withdrawal of the drug. However, in some cases, patients had changed the usage of metformin on their own initiative.

Latency times

The median latency time for ADRs that were reported in more than 1 % of patients was 1–6 days, except for pruritus with a median latency time of 16 days. An overview of ADR-specific latency times is shown in Table 4.

Discussion

ADRs

The results show that the majority of ADRs occur in the beginning of treatment with metformin. Females tend to have a higher risk of metformin-related ADRs. This is in line with earlier findings that demonstrate a higher risk of ADRs in females [14–18]. Although the occurrence of ADRs is the main reason for the withdrawal of metformin, more than half

Table 1 Characteristics of patients in the cohort

Characteristic	
Cohort size, no. of patients	2490
Average age, year (95 % CI)	59.2 (58.8–59.6)
Median age, year (IQR)	60.0 (52.4–66.8)
No. of males (%)	1478 (59 %)
No. of females (%)	1012 (41 %)
Average BMI (95 % CI)	29.6 (29.1–30.1)
Median BMI (IQR)	28.9 (25.9–32.1)
Indication for metformin[a]	
Diabetes mellitus, no. of patients (%)	2451 (98.4 %)
Weight loss, no. of patients (%)	8 (0.3 %)
Polycystic ovary syndrome, no. of patients (%)	6 (0.2 %)
Unknown indication, no. of patients (%)	7 (0.3 %)
Other, no. of patients (%)[b]	43 (1.7 %)
Concomitant drugs at baseline[c]	
Statins, no. of patients (%)	919 (37 %)
Selective beta blocking agents, no. of patients (%)	467 (19 %)
Platelet aggregation inhibitors excluding heparin, no. of patients (%)	392 (16 %)
Thiazides, no. of patients (%)	381 (15 %)
ACE inhibitors, no. of patients (%)	374 (15 %)
Angiotensin II antagonists, no. of patients (%)	349 (14 %)
Proton pump inhibitors, no. of patients (%)	342 (14 %)
Sulfonylureas, no. of patients (%)	196 (8 %)
Dihydropyridines, no. of patients (%)	192 (8 %)
Selective beta-2-adrenoreceptor agonists, no. of patients (%)	121 (5 %)
Blood glucose-lowering agents other than insulin, no. of patients (%)	219 (9 %)
Insulin and analogues, no. of patients (%)	97 (4 %)

95 % CI 95 % confidence interval, *IQR* interquartile range

[a] Because patients could report more than one indication, the total number of indications exceeds the total number of individual patients

[b] Other reported indications were often related to common co-morbidities in diabetic patients. An overview of all reported indications can be found in Online Resource 2

[c] Because patients could report more than one concomitant drug, the sum of the percentages of concomitant drugs can exceed 100 %. Only the most commonly used concomitant drugs are shown

of the patients undertake no action regarding metformin after the occurrence of an ADR. This suggests a relative low impact of ADRs on patients' quality of life. It seems that the positive effect of metformin outweighs the negative effects of ADRs when deciding to continue drug use. However, it is possible that withdrawal of metformin in between two questionnaires is associated with being lost to follow-up. Therefore, the reported percentage of patients who stopped the use of metformin within the first year of treatment might be an underestimation of the real percentage.

The majority of patients who experience ADRs consult a healthcare professional before dose reduction or withdrawal of metformin. Abdominal discomfort most often leads to withdrawal of metformin.

A surprisingly high number of patients (26 %) do not report recovery after drug withdrawal. However, this finding should be interpreted with caution due to the explained limitations of the study. The majority of patients (78 %) who continue the use of metformin recover or are recovering from ADRs during ongoing treatment. This finding is in line with the SPC which mentions that gastro-intestinal symptoms like nausea, vomiting, diarrhoea, abdominal pain and loss of appetite resolve spontaneously in most cases [1]. In the case of flatulence, this proportion is lower, suggesting that flatulence does not resolve spontaneously as often as the other symptoms do.

Patient characteristics

Although we found a statistically significant difference in age between the studied cohort and the SFK data, the absolute difference in age is small and probably not clinically relevant. The higher proportion of males who registered for the study

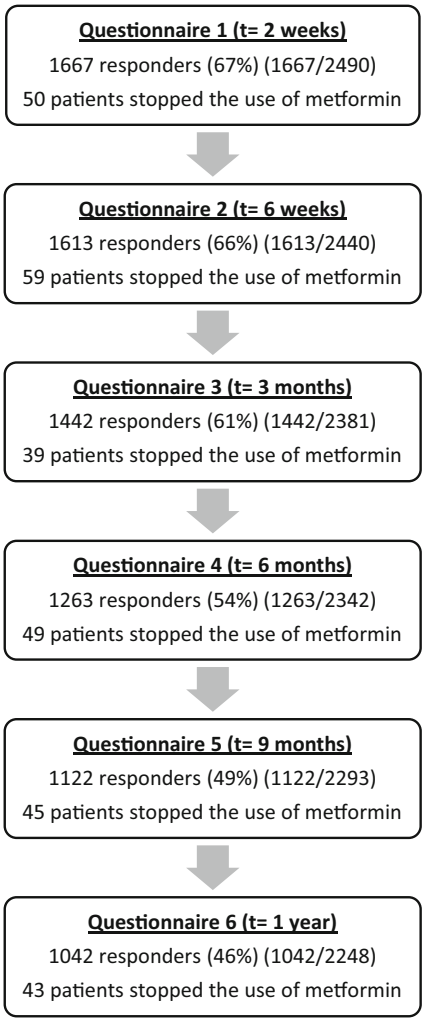

Fig. 1 Response rate for each questionnaire. Patients were allowed to fill in a questionnaire even if they had not completed the previous one

compared to the proportion of males in the SFK data indicates that males are more willing to participate in this intensive-monitoring study of metformin. This is in contrast with earlier findings in the LIM study of varenicline [19], where females were more willing to participate.

As can be expected, the most frequently reported indication for metformin is diabetes mellitus. A small proportion of patients use metformin for weight loss (0.3 %) or polycystic ovary syndrome (0.2 %), both are well-known off-label indications [20]. Given the diversity of the other reported indications, it is most likely that patients are not always aware of the indication for metformin.

Only a small proportion of patients (16.4 %) report information regarding weight and height. According to the international body mass classification (BMI), the study population can be classified as 'overweight (pre-obese)' with an average BMI of 29.6 kg/m^2. Being overweight is a well-known risk factor for new onset of T2DM. Other chronic conditions (e.g. cardiovascular diseases and nephropathy) are very common in patients with T2DM, and it can be expected that these patients often use concomitant drugs. Completing the questions in the questionnaires about concomitant drugs can be time-consuming, especially when a high number of concomitant drugs are used. This may cause underreporting of concomitant drug use. Therefore, we assume that the percentage of patients who use concomitant drugs is an underestimation of the real percentage. The Dutch guideline for general practitioners recommends to start treatment of T2DM with metformin monotherapy. By taking this guideline into account, the number of patients who are using other blood glucose-lowering agents and/or insulin and analogues is surprisingly high.

Response rate

The response rate of this study is the highest response rate received in the Lareb Intensive Monitoring programme so far. Altruism is the main motive for patients participating in

Table 2 ADRs reported in the study specified by gender

ADR	Frequency (*n*)	Incidence (*n*) in males	Incidence (*n*) in females	*p* value
All ADRs	34.5 % (858)	30.9 % (457)	39.6 % (401)	*<0.001*
Diarrhoea	14.8 % (369)	12.7 % (187)	18.0 % (182)	*<0.001*
Nausea	6.4 % (159)	3.6 % (53)	10.5 % (106)	*<0.001*
Abdominal discomfort	4.7 % (117)	4.0 % (59)	5.7 % (58)	*0.044*
Flatulence	3.7 % (91)	3.7 % (54)	3.7 % (37)	0.997
Headache	3.3 % (81)	2.6 % (38)	4.2 % (43)	*0.020*
Abdominal pain	2.3 % (57)	1.5 % (22)	3.5 % (35)	*0.001*
Dizziness	2.2 % (55)	1.9 % (28)	2.7 % (27)	0.197
Fatigue	2.0 % (51)	1.9 % (28)	2.3 % (23)	0.513
Constipation	1.5 % (37)	1.1 % (16)	2.1 % (21)	*0.044*
Pruritus	1.2 % (31)	1.4 % (21)	1.0 % (10)	0.339
Abdominal pain upper	1.1 % (27)	0.8 % (12)	1.5 % (15)	0.113
Dysgeusia	1.0 % (25)	0.9 % (14)	1.1 % (11)	0.731

Table 3 Action taken with drug after experiencing an ADR and the outcome of the reaction, depending on the action taken with the drug

Action or outcome	Diarrhoea	Nausea	Abdominal discomfort	Flatulence	Headache	All ADRs
Action taken with the drug after experiencing an ADR [% (*n*)][a]						
Patients who filled in this question	*n* = 366	*n* = 158	*n* = 116	*n* = 90	*n* = 81	*n* = 850
Drug withdrawn after consultation	7.4 % (27)	10.8 % (17)	10.3 % (12)	3.3 % (3)	8.6 % (7)	8.8 % (75)
Drug withdrawn on patient's own initiative	1.9 % (7)	1.3 % (2)	2.6 % (3)	1.1 % (1)	2.5 % (2)	2.6 % (22)
Dose reduced after consultation	6.6 % (24)	6.3 % (10)	7.8 % (9)	5.6 % (5)	4.9 % (4)	5.9 % (50)
Dose reduced on patient's own initiative	1.1 % (4)	0.0 % (0)	2.6 % (3)	0.0 % (0)	0.0 % (0)	0.9 % (8)
Other action	23.8 % (87)	23.4 % (37)	23.3 % (27)	27.8 % (25)	23.5 % (19)	30.9 % (263)
No action	59.3 % (217)	58.2 % (92)	53.4 % (62)	62.2 % (56)	60.5 % (49)	50.8 % (432)
Outcome of the ADR after stopping metformin use [% (*n*)][b]						
Patients who filled in this question	*n* = 51	*n* = 28	*n* = 17	*n* = 5	*n* = 11	*n* = 123
Recovered after withdrawal	27.5 % (14)	17.9 % (5)	23.5 % (4)	40.0 % (2)	27.3 % (3)	37.4 % (46)
Recovering after withdrawal	7.8 % (4)	21.4 % (6)	11.8 % (2)	20.0 % (1)	9.1 % (1)	16.3 % (20)
Did not recover after withdrawal	25.5 % (13)	39.3 % (11)	35.3 % (6)	40.0 % (2)	27.3 % (3)	26.0 % (32)
Unknown after withdrawal	39.2 % (20)	21.4 % (6)	29.4 % (5)	0.0 % (0)	36.4 % (4)	20.3 % (25)
Outcome of the ADR after continuing metformin use [% (*n*)][c]						
Patients who filled in this question	*n* = 346	*n* = 145	*n* = 106	*n* = 88	*n* = 77	*n* = 799
Recovered after continuing	49.1 % (170)	57.2 % (83)	51.9 % (55)	26.1 % (23)	46.8 % (36)	54.7 % (437)
Recovering after continuing	28.0 % (97)	24.8 % (36)	26.4 % (28)	30.7 % (27)	28.6 % (22)	23.0 % (184)
Did not recover after continuing	22.5 % (78)	17.9 % (26)	21.7 % (23)	43.2 % (38)	24.7 % (19)	21.8 % (174)
Unknown after continuing	0.3 % (1)	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.0 % (0)	0.5 % (4)

[a] Despite that a patient could report more actions through different questionnaires, only the action of highest importance was counted (level of importance: 'drug withdrawn after consultation' > 'drug withdrawn on patient's own initiative' > 'dose reduced after consultation' > 'dose reduced on patient's own initiative' > 'other action' > 'no action')

[b] Despite that a patient could report more outcomes through different questionnaires, only the outcome of highest importance was counted (level of importance: 'recovered after withdrawal' > 'recovering after withdrawal' > 'did not recover after withdrawal' > 'unknown after withdrawal')

[c] Despite that a patient could report more outcomes through different questionnaires, only the outcome of highest importance was counted (level of importance: 'recovered after continuing' > 'recovering after continuing' > 'did not recover after continuing' > 'unknown after continuing')

these kind of intensive monitoring studies [21]. This study demonstrates that intensive monitoring can also be used to study 'older' drugs to gather information about occurrence rate, latency time, management and outcome of ADRs in daily practice. There is a paucity of data concerning this kind of information about ADRs.

Table 4 Latency time of ADRs reported in ≥1 % of patients

ADR	Number	Latency time (days)		
		Median (IQR)	Mean (95 % CI)	Range
Diarrhoea	290	2 (1–12)	24 (17–31)	0–346
Nausea	124	3 (0–9)	19 (11–27)	0–244
Abdominal discomfort	78	4 (1–26)	78 (14–16)	0–357
Flatulence	65	2 (1–22)	29 (12–47)	0–358
Headache	65	3 (1–9)	16 (5–27)	0–254
Abdominal pain	43	1 (0–8)	21 (2–41)	0–351
Dizziness	41	6 (1–24)	20 (6–34)	0–273
Fatigue	42	5 (1–20)	20 (7–32)	0–241
Constipation	29	3 (1–8)	17 (2–32)	0–206
Pruritus	20	16 (1–87)	51 (19–83)	0–243
Abdominal pain upper	24	3 (0–38)	22 (7–37)	0–149
Dysgeusia	17	4 (1–23)	23 (−2–48)	0–221

Strengths and limitations of the study

Using patients as the main source of information has both its strengths and limitations. As the actual user of a drug and the person who experiences an ADR, the patient is the favoured source to obtain reliable information on start date of a drug, start date of an ADR, action taken with a drug and outcome of an ADR.

The most important limitation of this study is the fact that no causality assessment is performed on patient-reported ADRs. Although patients were asked to report only symptoms that were associated with the use of metformin, we cannot rule out that some of the reported symptoms are not caused by metformin. This particularly applies to symptoms with highly unlikely latency times. This should be kept in mind when interpreting the results of this study. A second limitation of the study is a high chance of lost to follow-up for patients who experience serious ADRs causing hospitalization or even death. These patients may be unable to complete the questionnaires in time.

The results on outcome of ADRs after withdrawal of metformin should be interpreted with caution. If the outcome of an ADR was reported within the same questionnaire in which the patient reported a withdrawal of metformin, it is possible that the patient had not yet recovered from the ADR during the moment the questionnaire was being completed, because the drug was withdrawn a short time before. To receive more reliable data on outcome of ADRs after drug withdrawal, future LIM studies should use additional follow-up questionnaires that focus on the outcome of ADRs. Another explanation is that there was no causal relation between the reported symptoms and the use of metformin.

In this study, patients were allowed to fill in questionnaires even though they had not completed the previous one. It can be expected that patients who have experienced an ADR are more motivated to fill in the questionnaire. This would give an overestimation of the occurrence rate of ADRs.

Conclusion

This study successfully obtained information about frequency, latency time, outcome and management of frequently occurring ADRs related to the use of metformin in daily practice. The median latency time of the most frequently reported ADRs is less than 7 days, with exception of pruritus. In the majority of cases, no action was taken according to metformin after the occurrence of ADRs. The findings are in line with the Summary of Product Characteristics of metformin and confirm that the safety profile of metformin in daily practice is relatively safe. This study demonstrates that, besides the monitoring of new drugs, intensive monitoring can also be used to investigate older drugs to gather information about occurrence rate, latency time, outcome and management of ADRs.

Acknowledgments The support of pharmacies in the Netherlands is very much appreciated. We want to thank all the patients who participated in this study, without whom this study would have not been possible.

Contributions of authors LH and EP are responsible for the study conception and planning. LJ and EP are responsible for the acquisition, analysis or interpretation of data. LJ is responsible for the drafting of the manuscript. LH and EP are responsible for the critical revision of the manuscript.

Compliance with ethical standards

Funding No funding source.

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard. Privacy policy agreement was obtained from all individual participants included in the study

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