

## BRIEF REPORT

# Adverse drug event patterns experienced by patients with diabetes: A diary study in primary care

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## Abstract

**Purpose:** Little is known about adverse drug events (ADEs) experienced over time during chronic drug use. The purpose of this study was to assess ADE patterns experienced by patients with diabetes.

**Methods:** Patients who received an oral glucose-lowering drug completed a daily diary for 13 weeks. The diary asked for experienced symptoms and whether patients related these symptoms to any drug they used. Summaries of Product Characteristics were used to check whether the ADEs were known adverse drug reactions (ADRs) of the drugs used. Patterns of weekly occurring ADEs were assessed with descriptive statistics.

**Results:** We included 78 patients. Almost half of them reported at least one ADE (N = 36; 46%). In total, 80 ADEs were reported. Of these ADEs, 71 (90%) were known ADRs. ADEs lasted less than 1 week in 27 cases (34%) and between 2 and 12 weeks in 15 cases (19%). The remaining ADEs fluctuated (16 cases; 20%) or persisted (22 cases; 28%) during the entire study period.

**Conclusions:** ADEs experienced by patients with diabetes can fluctuate or persist over long periods of drug use.

## KEYWORDS

diabetes mellitus, drug-related side effects and adverse reactions, patients, pharmacoepidemiology, primary health care, type 2

## 1 | INTRODUCTION

Possible adverse drug reactions (ADRs) reported by patients (in this article referred to as adverse drug events [ADEs]) are common. We previously found that 27% of diabetes patients experienced at least one ADE in the past 4 weeks at a random moment of treatment stage.<sup>1</sup> ADEs are most likely to occur at treatment start, that is, within days or weeks after treatment initiation.<sup>2-5</sup> However, ADEs can also

emerge during chronic treatment because of changes in the patient's susceptibility or situation, such as a decrease in kidney function or a drug-drug interaction.<sup>6</sup>

In Europe, information about ADRs is provided in the Summary of Product Characteristics (SmPC) of a drug. This may include details about the frequency of the reaction and time of occurrence after treatment initiation. Occasionally, information is provided on the expected duration, for example, when reactions are usually

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transient and expected to resolve within a short period of time. Postmarketing studies have illustrated that some ADEs are experienced by patients for a short time whereas others can persist during treatment.<sup>2-4,7</sup>

More knowledge about ADE patterns over time is important for guideline developers, drug regulators, and pharmaceutical industry. This is also much needed to inform patients and health care providers and help them to detect, mitigate, and deal with ADEs better. Not knowing what to expect, ADEs may lead to unneeded or unguided reduction or discontinuation of drugs. Our aim was to assess ADEs as experienced over time by patients with diabetes.

## 2 | METHODS

### 2.1 | Design

A post hoc cohort study was conducted using diary data previously collected for the validation of a patient-reported ADE-questionnaire.<sup>8</sup> Informed consent was obtained from all participants.

### 2.2 | Participants

Adults being dispensed at least one oral glucose-lowering drug were recruited via pharmacies in the north of the Netherlands. The dispensing of this drug was used as proxy for a diagnose of type 2 diabetes. No restrictions were made on treatment duration or concomitant treatment, thereby including a heterogeneous group of patients. Recruitment procedures have been described in detail previously.<sup>8</sup> Patients were included if they could provide an e-mail address, had internet access, and returned a completed consent form. This recruitment method implies that patients were using chronic medication at the time of data collection, possibly including other drugs aside from the oral glucose-lowering drug, or could even start with a new drug during follow-up.

### 2.3 | Data collection

Patients were asked to complete on a daily basis a paper-based diary for a period of 13 weeks. An open-ended question asked for any symptoms they had experienced each day. A follow-up closed-ended question in the diary asked whether or not the patient thought the symptom was related to medication use. There is a difference between the definition of an ADR and an ADE in respect to whether or not formal causality assessment is applied.<sup>9</sup> The symptoms that patients concerned to be possibly related to the use of their drugs were considered as ADEs since no formal causality assessment was done in this study. These ADEs were classified according to the Medical Dictionary for Regulatory Activities System Organ Class (MedDRA SOC).<sup>10</sup> At the end of the period, patients completed a structured questionnaire to collect background characteristics and information

### KEY POINTS

- Approximately half of the adverse drug events (ADEs) reported by patients were fluctuating or persistent over a period of 13 weeks, whereas a third of such ADEs had a short duration of not more than 1 week.
- Health care providers should pay attention to fluctuating and persistent ADE patterns in patients on chronic medication.

about the drugs they had used in the study period, including prescription drugs and self-medication.<sup>11</sup>

### 2.4 | ADE-drug relation

All drugs the patient had reported to use were checked for known ADRs as referred in the most recent SmPC identified through the medicines information repository of the Dutch Medicines Evaluation Board (<https://www.geneesmiddeleninformatiebank.nl/en>). Reported ADEs that were identified in these SmPCs were documented as a possible ADE-drug relation.

### 2.5 | ADE patterns

ADE patterns were described as occurring in each of the 13 weeks during the study period. Occurrence could result in the following patterns: (a) short ADE episode, an ADE was only reported in 1 of the 13 weeks; (b) intermediate ADE duration, an ADE was reported in at least 2 but less than 13 consecutive weeks; (c) fluctuating pattern, an ADE was reported during at least 2 nonconsecutive weeks; and (d) persisting ADE, an ADE was reported in all 13 weeks.

### 2.6 | Statistical analysis

Descriptive statistics were used to describe the included population, the occurrence of ADEs, possible ADE-drug relations (ie, the number of reported ADEs that are known in SmPCs of any of the drugs the patients use), and ADE patterns (ie, the number of short, intermediate, fluctuating, and persisting patterns).

## 3 | RESULTS

Seventy-eight patients completed the study. These patients were on average 65 years old (SD: 9, range 42–82) and 47 (60%) were male. Thirty-six patients (46%) reported at least one ADE during the 13 weeks. In total, 80 ADEs were reported, most of which belonged to gastrointestinal disorders, nervous system disorders, and musculoskeletal and connective tissue disorders (Table 1). Of the 36 patients who reported an ADE, 19 (53%) also reported at least one symptom

**TABLE 1** Frequency of ADE patterns per MedDRA System Organ Class (SOC)

MedDRA SOC level	Total Number	Short	Intermediate	Fluctuating	Persisting
Blood & lymphatic system disorders	0				
Cardiac disorders	1			1	
Congenital, familial, & genetic disorders	0				
Ear & labyrinth disorders	1				1
Endocrine disorders	0				
Eye disorders	1				1
Gastrointestinal disorders	22	7	3	6	6
General disorders and administration site conditions	7	2	1	2	2
Hepatobiliary disorders	0				
Immune system disorders	0				
Infections & infestations	0				
Injury, poisoning, & procedural complications	0				
Investigations	0				
Metabolism & nutrition disorders	2			1	1
Musculoskeletal & connective tissue disorders	13	3	5	2	3
Neoplasms benign, malignant, and unspecified (incl. cysts & polyps)	0				
Nervous system disorders	14	7	2	1	4
Pregnancy, puerperium and perinatal conditions	0				
Psychiatric disorders	3	1		2	
Renal & urinary disorders	2		1		1
Respiratory, thoracic, & mediastinal disorders	3	3			
Skin & subcutaneous tissue disorders	9	3	2	1	3
Social circumstances	0				
Surgical and medical procedures	0				
Vascular disorders	1		1		
Not classified <sup>a</sup>	1	1			
Total number	80	27	15	16	22

Abbreviations: ADE, adverse drug event; MedDRA, Medical Dictionary for Regulatory Activities.

<sup>a</sup>One ADE was not classified because of an unclear description of the ADE.

during the 13 weeks, which they did not consider to be an ADE. Of the 42 patients who did not report an ADE, 17 (41%) reported at least one symptom in the diary.

### 3.1 | ADE-drug relation

Patients who reported an ADE used on average six drugs (range 1-17). For eight of the 80 ADEs, the patient used no drugs for which the reported ADE was stated in the SmPC. For one ADE, a link with the used drug was questionable given the patient's description of the ADE. In all other cases (N = 72; 90%), patients used at least one drug that had the reported ADE in the SmPC (Appendix S1). For example, patients reporting musculoskeletal and connective tissue ADEs often used statins, and patients reporting gastrointestinal ADEs often used metformin. In many cases, patients used multiple drugs that had the reported ADE as a known ADR.

### 3.2 | ADE patterns

Of the 80 reported ADEs, 27 (34%) were short episodes of not more than 1 week, 15 (19%) had an intermediate duration, 16 (20%) showed a fluctuating pattern, and 22 (28%) persisted during the 13-week study period. Nervous system disorders had mostly a short episode, whereas musculoskeletal and connective tissue disorders were mostly of intermediate duration. For the gastrointestinal disorders, short episodes, fluctuating patterns, and persisting patterns were seen to a similar extent (Table 1).

Short episodes were often ADEs reported for periods of 1 to 3 days and were most often reported in the first two study weeks. The duration for intermediate ADEs ranged from 2 to 9 weeks, and 6 (40%) were reported for the first time in the first week. In most of the fluctuating patterns, the ADE was experienced at 1 to 3 days, whereas the number of weeks in which the ADE was reported ranged from 2 to 12 with a median of 6 weeks. In four

cases, the ADE was reported on more than 20 days in the study period. Most of the persisting patterns were reported during 5 to 7 days in all weeks (Appendix S2).

## 4 | DISCUSSION

Almost half of the patients reported at least one ADE during the 13 study weeks, with a total of 80 ADEs. The majority of the ADEs could be identified as a known ADR of one or more of the drugs the patient used. Most commonly, we observed short duration, fluctuating or persistent gastrointestinal ADEs, short duration nervous system ADEs, and intermediate duration musculoskeletal ADEs.

The percentage of patients reporting possible ADEs in our study is relatively high compared with previous studies.<sup>1,2,11</sup> This may in part be due to the follow-up period of 13 weeks, in which many short ADE episodes can be detected. More than 30% of the ADEs were for short episodes. The number may also be high because of the prospective data collection using a diary. Many patients used multiple drugs that can cause possible ADEs. It can therefore be difficult for patients to attribute a symptom to the drugs they use. Keeping a diary might help to clarify this. Timing relationships are important for patients to assess possible ADEs.<sup>12</sup> On the other hand, it could be that patients were more active in keeping the diary in the first week of the study. Several short episodes were reported in the first 2 weeks. This could imply overreporting in the first weeks but also underreporting after the first weeks. For future studies, it is advised to use electronic diaries to be able to send reminders. This will reduce the chance of underreporting. Remarkable, however, was the high percentage of experienced ADEs that could be linked to one of the drugs the patients were using. This suggests that patients were able to identify symptoms that are related to a drug, although they may still attribute unrelated symptoms to their drugs.

Prospective monitoring studies in patients starting new drugs have shown that patients may continue to use a drug despite perceiving a possible ADE and without taking further action.<sup>2-4</sup> Our study adds to this knowledge that patients on chronic medication may experience persisting ADEs over periods of at least 13 weeks, whereas other ADEs may come and go during considerable periods of drug use. Such fluctuation of ADEs has been reported before by patients receiving drugs for chronic heart failure.<sup>7</sup> It indicates that patients are willing to accept a wide range of symptomatic ADEs or are able to deal with such ADEs and that experienced ADEs are not necessarily a reason for patients to discontinue treatment.<sup>3</sup> Future studies are needed to assess the influence of the experienced severity of the ADE on patterns and actions taken by patients. Our study illustrates that patients are willing to provide information about the duration of ADEs, but there could be selection bias among the participants.<sup>13</sup> In addition to prospective monitoring studies, it would therefore be useful to collect information about ADE patterns in randomized controlled trials. Ultimately, information about ADE timing should be considered for inclusion in SmPCs.

An important strength of our study is that we used a daily diary for patients to report possible ADEs. Although we are not sure whether

patients completed the diary on a daily basis, the use of a diary reduces recall problems. We asked patients to report any symptoms and subsequently asked whether they thought the symptom was related to any of the drugs they used. This was previously suggested as a more reliable way to question patients about ADEs.<sup>11</sup>

The most important limitation is the small sample size in our study.<sup>8</sup> Regarding age, the participants appear similar to the average primary care diabetes population in the Netherlands but a higher proportion of males was included. Furthermore, we did not have diary data on lifestyle or medication changes, which may influence ADE patterns.

In conclusion, ADEs experienced by patients with diabetes can fluctuate or persist over long periods of drug use. It is important that health care providers are aware of this and try to monitor ADEs better by regularly informing and asking their patients on chronic medication about ADEs during routine visits.

## ETHICS STATEMENT

The Medical Ethics Committee of the University Medical Center Groningen (METc UMCG) in the Netherlands determined that ethical approval was not needed for this study (reference number M12.112446).

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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