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Comparing Adverse Event Rates of Oral Blood Glucose-Lowering Drugs Reported by Patients and Healthcare Providers

A *Post-Hoc* Analysis of Observational Studies Published between 1999 and 2011

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Abstract

Background: Non-serious symptomatic adverse drug events (ADEs) affect the real benefit-risk ratio of a drug. Currently, such ADEs are quantified in different ways, often using reports from a healthcare provider or patients, resulting in large variations in estimated rates. Several studies showed that patients report bothersome or symptomatic ADEs more frequently than providers, but no comparisons to an external reference or gold standard have been made.

Objective: We conducted a literature review to assess the agreement and concurrent validity of healthcare provider- and patient-oriented methods for quantifying symptomatic ADEs of oral blood glucose-lowering drugs in patients with type 2 diabetes mellitus.

Methods: We systematically searched MEDLINE and EMBASE databases for observational studies reporting on rates of ADEs in patients treated for type 2 diabetes that were published between 1999 and 2011. We included nine observational studies reporting absolute rates of symptomatic ADEs in patients receiving monotherapy. We calculated 95% confidence intervals and assessed agreement between rates observed with different methods. We assessed concurrent validity using the range noted in the Summary of Product Characteristics (SPC) as the gold standard.

Results: A comparison of rates reported by patients and providers was only possible using three studies of metformin that assessed mainly gastrointestinal (GI) ADEs. Provider-oriented methods by means of medical record review gave lower rates for abdominal pain (0.6–3.7%), dyspepsia (1.3–2.8%) and constipation (0.6–1.0%) than a patient questionnaire method (8.5%, 11.9% and 20.7%, respectively). For diarrhoea, the patient-reported rate (5.2%) was in agreement with the provider-based rates (1.6–7.6%). The

majority of the rates reported by providers and patients were not corresponding with the ranges in the SPC. For GI ADEs the rates were all lower, whereas for lactic acidosis and hypoglycaemia the rates were higher.

Conclusion: Although it has repeatedly been proposed that patients' reports on safety should be incorporated with providers' reports, especially for symptomatic ADEs, the number of observational studies using patient-oriented methods for assessing ADEs other than hypoglycaemia are limited. Provider-based measurement tended to underestimate symptomatic ADEs. Patient-oriented methods seemed to give ADE rates that were closer to the rates reported in the SPC.

Background

There is a need for collecting reliable information on safety issues throughout a drug's lifecycle.[1] Much attention is being paid to the assessment of serious, life-threatening adverse drug events (ADEs), whereas non-serious, symptomatic ADEs are being neglected.[2,3] The proportion of patients perceiving such ADEs, however, is relatively high.[4,5] Symptomatic ADEs may substantially affect the patients' quality of life and their adherence to treatment, and thus the real benefit-risk ratio of a drug.[3] Current regulatory guidelines do not provide any recommendations on the methods that should be used to assess and quantify symptomatic ADEs.[6-9]

Existing methods of safety assessment in postmarketing studies consist of healthcare provider-oriented methods, including medical record and claims data review; methods based on laboratory data; and patient-oriented methods, including questionnaires and diaries.[6,10] For quantification of non-serious symptomatic ADEs, laboratory data are too limited.[11] Also, provider-based methods may be too limited.[11] When providers obtain, interpret and report ADEs, they can undervalue or underestimate the frequency of symptomatic ADEs in comparison with patients' reporting.[12] Patient-oriented methods appear to be more suitable for assessing symptomatic ADEs, since tolerability to such ADEs depends on the individual disposition of patients.[5] Such methods have been criticized for feasibility issues and difficulties with causality linkage of reported ADEs to the drug, but there seems to be little evidence for this.[13,14] Several studies found that patients report ADEs more frequently than providers, especially with respect to bothersome symptoms.[12,15,16] The question remains what the true incidence of the ADEs is. One could consider the safety information in the Summary of Product Characteristics (SPC) as the gold standard, since this is based on the results from all the available sources and incorporates all known information on ADE rates.[17] There seem to be no studies, however, comparing rates measured with various methods to the rates documented in the SPC.

We aimed to assess the agreement and concurrent validity of provider- and patient-oriented methods to quantify symptomatic ADEs of oral blood glucose-lowering medication by comparing these rates with each other and with ranges noted in the SPC. We selected glucose-lowering drugs for type 2 diabetes mellitus as a case, since these drugs are widely prescribed and can cause a broad range of symptomatic ADEs. We specifically focused on ADE rates found in observational studies, since these show the safety profile of drugs in everyday practice.[18] We hope this will contribute to improved guidance on how best to collect valuable and necessary data on these ADEs.

Methods

Study Selection

We systematically searched MEDLINE and EMBASE databases for observational studies

reporting on rates of ADEs in patients treated for type 2 diabetes, and that were published between 1 January 1999 and 1 January 2011 in English, German, French, Spanish or Dutch languages. The search strategy included the combination of three domains, using MeSH-, subheading- and free-text terms for 'adverse events', 'observational study designs' and 'drug therapy', combined with 'diabetes'. This search resulted in 13 514 publications, of which we identified 941 articles for full-text screening. For this study, we identified observational studies in adult patients with type 2 diabetes if they (i) included at least one group of patients receiving monotherapy with an oral blood glucose-lowering drug or one group with at least 90% of patients receiving such monotherapy; (ii) reported the rate of at least one type of symptomatic ADE; and (iii) used either a healthcare provider or a patient-oriented method for assessing the ADE. A symptomatic, non-serious ADE was defined as ''any unfavourable and unintended sign or symptom that may be present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment and which was not life-threatening, requiring hospitalization or resulted in significant disability or death''.[9] Discontinuation due to intolerance was not considered as assessing an ADE rate.

For the SPC we first searched European Public Assessment Reports from the European Medicines Agency (EMA) website.[19] When SPCs were not available on the EMA website because of a national registration procedure, we searched the Dutch Medicines Evaluation Board[20] and UK electronic Medicines Compendium websites.[21]

Data Abstraction

Data were abstracted from the selected publications by two reviewers using a standardized data abstraction form. Discrepancies were resolved by consensus.

The following information was abstracted: drugs administered (including dosages); methods used to quantify ADEs; rates and definitions of identified ADEs; probability of causality; and methods of causality assessment. For the assessment of study quality we abstracted data on inclusion and exclusion criteria for the patient population and their sociodemographic (age, sex, ethnicity) and clinical (duration and severity of diabetes, co-morbidities and co-medications) characteristics; sample size, duration of follow-up, number lost to follow-up and response rate. In addition, data on general study characteristics (study design, study country, setting and funding source) were abstracted.

From the SPC we abstracted data on frequency ranges of labelled ADEs noted in section 4.8 'Undesirable effects' and whenever referred to, section 4.4 'Special warnings and precautions for use'.

Methods of Adverse Drug Event (ADE) Measurement

We classified methods for ADE measurement in two categories: (i) [healthcare] provider-oriented, where ADEs were collected by or through healthcare providers using case report forms, medical records or related administrative databases; and (ii) patient-oriented methods, where the data were collected directly from patients using open and/or closed questionnaires, checklists or diaries.

Rates of ADEs Identified

Reported ADEs were classified on the lowest level based on Common Terminology Criteria for Adverse Events (CTCAE) classification version 4.02, which is concordant with MedDRA® version 12.0.[22] Absolute rates of ADEs were abstracted from the studies that were comparable to those noted in the SPC, i.e. crude incidence rates not calculated against placebo or other comparators.[17]

Methodological Quality

We assessed the methodological quality of the included studies in relation to medication safety measurement using a modified version of the Newcastle-Ottawa scale for observational cohort studies.[23] This scale allows the assignment of stars for various items in three domains, i.e.

adequate patient selection, comparability and outcome assessment. Since we focused on measurement of absolute rates of ADEs, we removed the items related to comparability. Cohort studies could thus receive stars for (i) representativeness of the exposed cohort; (ii) secure ascertainment of exposure; (iii) demonstration that outcome was not present at start; (iv) clear definition and specified time period for the outcome; (v) follow-up time of at least 3 months; and (vi) at least 80% follow-up for studies up to 11 months or 60% for follow-up periods of at least 1 year. Cross-sectional studies could receive stars for (i) representativeness of the exposed cohort; (ii) secure ascertainment of exposure; (iii) clear definition and specified time period for the outcome; and (iv) response rate of at least 70%. A study was classified as high quality when assigned 5–6 stars for cohort or 4 stars for cross-sectional studies; as medium quality when assigned 3–4 stars for cohort or 2–3 stars for cross-sectional studies; and as low quality when assigned 0–2 stars for cohort or 0–1 star for cross-sectional studies.

Data Analysis

We analysed ADE rates identified per treatment arm. In accordance with the categories provided in the SPC, we categorized the rates of ADEs as follows: (i) very common, ≥10%; (ii) common, ≥1%, <10%; (iii) uncommon, ≥0.1%, <1%; (iv) rare, ≥0.01%, <0.1%; and (v) very rare, <0.01%. We calculated 95% confidence intervals (CIs) for all ADE rates.

To assess agreement of provider-oriented methods with patient-oriented methods, we examined whether the rate of the same ADE reported by two methods fell into the same category and whether the 95% CIs were overlapping. To assess concurrent validity, we compared rates of ADEs measured by either method to the range noted in the SPC. We classified the rates as (i) fully corresponding to the SPC when both the point estimate and the 95% CI fell within the correct category; (ii) partially corresponding when at least one side of the 95% CI fell within the correct category; and (iii) not corresponding if neither the point estimate nor the 95% CI fell within the correct category. Proportions of specific ADE rates identified with provider- and patient-oriented methods are presented according to these classes.

Since the rates of ADEs might be reported over different observation periods, we took into account the time period within which each ADE was measured. Calculations were conducted after excluding low-quality studies.

Results

We identified 79 observational studies that reported rates for non-serious ADEs of oral blood glucose-lowering drugs in adult patients with type 2 diabetes. Of these, nine publications met our inclusion criteria (figure 1).[24-32] Seven studies reported on treatment with metformin, one of which tested two different formulations of metformin. The remaining two studies reported on treatment with glibenclamide and acarbose (table I). Five studies used provider-oriented methods, whereas four studies used patient-oriented methods (table I). In the studies with provider-oriented methods, 31 rates of symptomatic ADEs were presented that could be attributed to the drug treatment of the study. Two of 31 rates did not fit any of the CTCAE terms ('blood in stool' and 'faecal abnormality'). Patient-oriented methods were limited to the measurement of either hypoglycaemia or gastrointestinal (GI) ADEs (table I). In total, 12 rates of symptomatic ADEs were presented, two of which ('bowel-related pain' and 'steatorrhoea-like stools') did not fit any of the CTCAE terms.

Eight of the studies were classified as medium quality and one study as low quality (table I). Four studies assessed ADE rates over a period of approximately 1 year, whereas the other studies evaluated shorter periods. Four studies assessed ADE rates in the first period after initiation of the drug, whereas the other studies also included prevalent users. Doses of medications reported did not exceed those recommended in the SPC, but information on dosage was not specified in four studies. Treatment adherence and causality assessment were not documented in any of the studies.

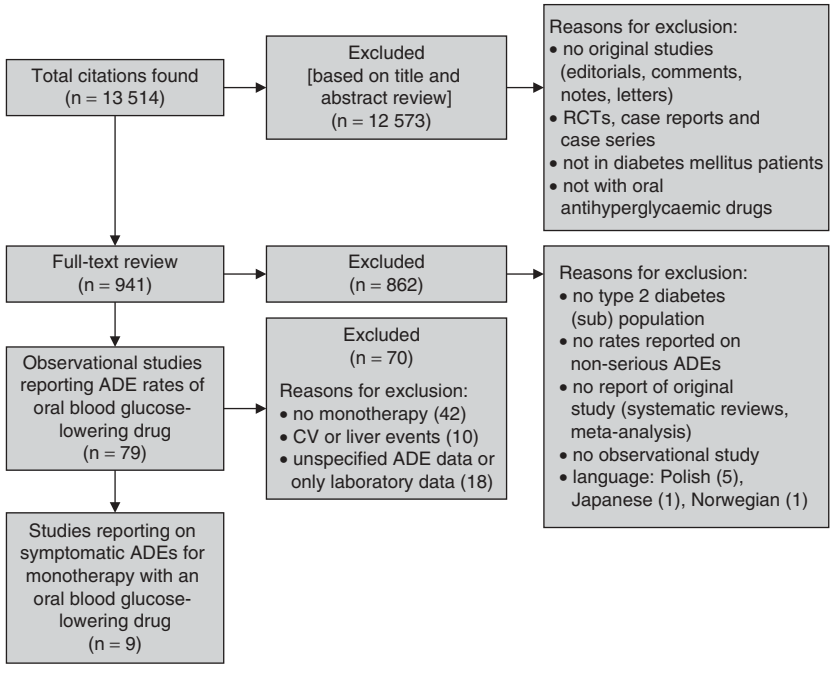

Fig. 1. Study flow diagram. **ADE** = adverse drug event; **CV** = cardiovascular; **RCTs** = randomized controlled trials.

Agreement between Provider- and Patient-Oriented Methods

For patients treated with metformin, a comparison of GI ADE rates was possible between provider-oriented methods (two studies including three treatment arms) and a patient-oriented method (one study), since they assessed these ADEs over a similar time period (table I). The study with the patient-oriented method included a small number of patients with concomitant use of a sulfonylurea drug (7%) or acarbose (1%).[28] For hypoglycaemia, the comparison was hampered by differences in population and period for ADE measurement. For the other drugs, no comparison was possible.

There were four specific GI ADEs reported for patients taking metformin using both methods, i.e. diarrhoea, constipation, abdominal pain and dyspepsia (figure 2). For diarrhoea, all three provider-based rates were in the category 'common', with point estimates ranging from 1.6% to 7.6%. The patient-reported rate was 5.2%, falling into the same category (95% CI 2.2, 8.2; overlapping with two of the three provider-based intervals). For constipation, the two provider-based rates were 'uncommon' (0.97% and 0.6%), whereas the patient-reported rate was 'very common' (20.9%; 95% CI 15.4, 26.4; not overlapping with intervals of provider-based rates). For abdominal pain, one provider-based rate was in the category 'uncommon' (0.6%), whereas two other provider-based rates were 'common' (1.6% and 3.7%). The patient-reported rate was in the same category (8.5%; 95% CI 4.7, 12.3) but with CIs not overlapping with the intervals of the provider-based rates. For dyspepsia, the provider-based rates were in the category 'common', ranging from 1.3% to 2.8%, whereas the patient-reported rate was in the category 'very common' (11.9%; 95% CI 7.5, 16.3; not overlapping with intervals of provider-based rates).

For hypoglycaemia in patients treated with metformin, the provider-oriented measurement during a mean time of 10 days in a high-risk hospitalized patient population showed a rate of

Table I. Characteristics of included studies reporting on monotherapy treatment groups

First author	Country	Design	Treatment drug	Users; population	Method	Quality	ADE focus and ADEs reported	Sample size	Time period
Asche et al.[24]	US	RC	Metformin	Initial; >65 y	Provider (records)	Medium	Five drug-specific: diarrhoea, nausea, abdominal pain, dyspepsia, lactic acidosis	2138	13 mo
Blonde et al.[25]a	US	RC	Metformin-XR	Initial or switched	Provider (records)	Medium	Any GI-specific: diarrhoea, nausea, dyspepsia, abdominal pain, constipation, vomiting, abdominal distension, faecal abnormality, blood in stool, flatulence	310	~12 mo
Blonde et al.[25]b			Metformin	Initial	Provider (records)	Medium	Any GI-specific: diarrhoea, nausea, dyspepsia, abdominal pain, constipation, vomiting, abdominal distension, faecal abnormality, blood in stool, flatulence	158	~12 mo
Feher et al.[26]	UK	RC	Metformin-XR	Switched	Provider (case notes)	Medium	Overall GI ADEs	22	6 mo
Redondo-Capafons et al.[27]	Spain	PC	Metformin	Any use; high-risk hospital population	Provider (records)	Low	Any ADE: diarrhoea, hypoglycaemia	135	10 d
Bytzer et al.[28]	Australia	CS	Metformin[c]	Any use	Patient (checklist questions)	Medium	Nine GI-specific: abdominal pain, GI reflux, dyspepsia, stomach pain, bowel-related pain, constipation, diarrhoea, steatorrhea-like stool, faecal incontinence	211	12 mo
Miller et al.[29]	US	CS	Metformin	Any use	Patient (questions)	Medium	Hypoglycaemia	35	2 mo
Chan et al.[30]	Asia-Pacific	CS	Metformin	Any use	Patient (checklist questions)	Medium	Hypoglycaemia	314	6 mo
Guagnano et al.[31]	Italy	PC	Glibenclamide	Any use	Patient (diaries)	Medium	Hypoglycaemia	330	11 mo
Spengler et al.[32]	Germany	PC	Acarbose	Initial	Provider (CRF)	Medium	Only hypoglycaemia for monotherapy	4232	3 mo

a Metformin-XR treatment arm presented in Blonde et al.[25]

b Metformin treatment arm presented in Blonde et al.[25]

c Fourteen patients had concomitant use of a sulfonylurea drug and two had concomitant use of acarbose.

ADE = adverse drug event; **CRF** = case report form; **CS** = cross-sectional; **GI** = gastrointestinal; **PC** = prospective cohort; **RC** = retrospective cohort; **XR** = extended release.

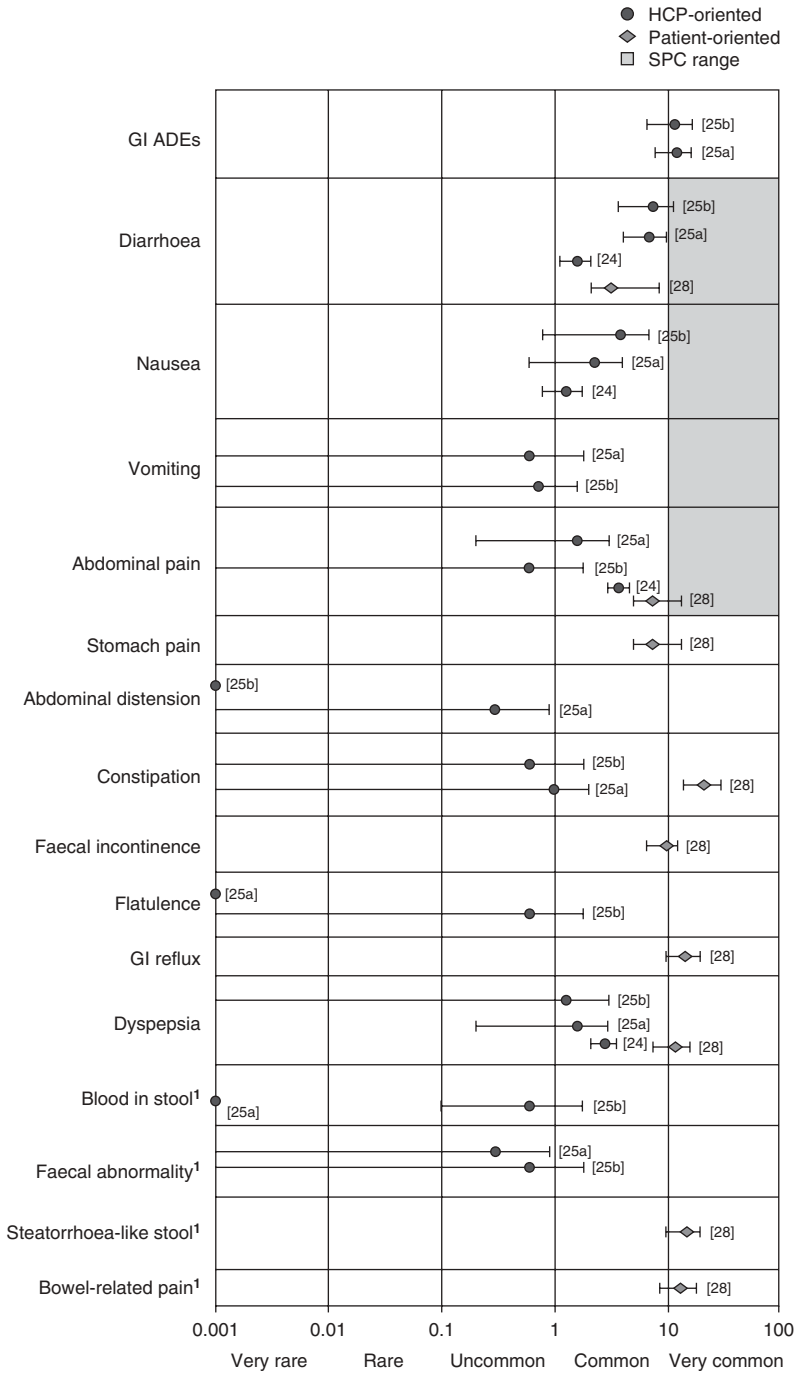

Fig. 2. Rates (point estimates with 95% CIs) of gastrointestinal adverse drug events (GI ADEs) for metformin from medium-quality studies presented in table I. Logarithmic scale divided in categories used in the Summary of Product Characteristics (SPC). The numbers in this figure are references, where reference 25 reports separate ADE rates for metformin extended release (a) and metformin (b). **1** ADEs that do not fit any Common Terminology Criteria for Adverse Events classification. **HCP** = healthcare provider.

6.0% (95% CI 3.0, 9.0), whereas patient-based measurement in outpatient populations resulted in a rate of 8.6% (95% CI 0, 17.6) over a period of 3 months and 24.2% (95% CI 19.5, 28.9) over a period of 6 months.

Comparison with ADE Rates in the Summary of Product Characteristics

Overall, there were 13 specific ADE rates reported by providers and 2 reported by patients for which a comparison could be made with a range mentioned in the SPC; ADE rates assessed over a mean period of 10 days in a high-risk population in a low-quality study[27] were not compared with the SPC. According to the SPC of metformin, GI ADEs of diarrhoea, nausea, vomiting, abdominal pain and loss of appetite are all 'very common', i.e. each may occur in >10% of the exposed patients. Provider-oriented methods gave lower point estimates for diarrhoea, nausea, vomiting and abdominal pain, all of which were assessed over a period of approximately 1 year (11 ADE rate point estimates [see figure 2]). Also, the patient-oriented method gave point estimates for diarrhoea and abdominal pain that were lower than the SPC rates (2 ADE rate point estimates [see figure 2]). According to the SPC, lactic acidosis is 'very rare' for patients taking metformin, i.e. occurs in <0.01%. One study using a provider-oriented method found a rate of 0.3% (95% CI 0.1, 0.5).

As mentioned previously, three studies reported rates of hypoglycaemia for metformin, which is not specified as an ADE in the SPC. For acarbose, the rate of hypoglycaemia is stated to be zero in the SPC, whereas a provider-based rate of 0.03% over a period of 3 months (95% CI 0, 0.06) was reported. Some of the other ADEs mentioned in the SPC for acarbose were reported, namely flatulence and diarrhoea, but no rates were presented for the monotherapy group. For glibenclamide, hypoglycaemia is noted as an ADE, but the rate is not specified in the SPC. In a study using patient diaries, the reported hypoglycaemia rate was 21.8% over a period of 11 months (95% CI 17.3, 26.3).

Overall, of the 13 provider-based rates, 11 (85%) were not corresponding with the SPC range and the remaining three were partially corresponding (table II). Of the two patient-reported rates, one was partially corresponding and another was not corresponding to the SPC. Since most of these ADE rates came from studies using a 9- to 15-month period of evaluation, the correspondence with the SPC is similar when limiting the comparison to this time period.

Discussion

Our indirect comparison of ADE rates showed that provider-oriented assessment methods by means of medical record review gave considerably lower rates for abdominal pain, dyspepsia and constipation than a patient questionnaire method. For diarrhoea, the provider-based rate was in agreement with the patient-oriented rate. The majority of the rates reported by providers and patients were not fully corresponding with the ranges mentioned in the SPC. For GI ADEs the rates were all lower, whereas for lactic acidosis and hypoglycaemia the rates were higher.

Table II. Adverse drug event rates per measurement method compared with ranges mentioned in the Summary of Product Characteristics (SPC)

Measurement method (time period)	Drug studied	No. of rates not corresponding with SPC (lower/higher)	No. of rates partially corresponding with SPC	No. of rates fully corresponding with SPC
Provider-oriented total		**11**	**2**	**0**
Specific GI (~12 mo)	Metformin	10 (lower)	1 (lower)	
Lactic acidosis (~12 mo)	Metformin	1 (higher)		
Hypoglycaemia (3 mo)	Acarbose		1 (higher)	
Patient-oriented total		**1**	**1**	**0**
Specific GI (12 mo)	Metformin	1 (lower)	1 (lower)	

GI = gastrointestinal.

We could include only nine studies reporting symptomatic ADEs in monotherapy groups using either provider- or patient-oriented methods. Many observational studies, including prescription event-monitoring studies, assess ADEs in patients using combinations of drugs, or report ADEs at drug class level. In addition, ADE assessment is frequently limited to laboratory results. None of the included studies conducted a direct comparison between different methods of ADE assessment. For cancer treatment, there have been a few studies that directly compared specific ADE rates as reported by providers and patients. In a study focusing on ADEs in lung cancer patients receiving chemotherapy, it was found that providers reported symptomatic ADEs less frequently and later than patients.[12] Also, from trials evaluating treatment for prostate cancer, it was concluded that physicians often underestimate ADEs perceived by patients.[15,33] Similar findings have been reported in studies looking at the reporting of potential ADEs for anti-rheumatic drugs[16,34] and recently marketed drugs,[35] as well as studies regarding symptoms and quality of life, where physicians underestimate or underreport patients' symptoms in various clinical domains.[36,37]

There are pros and cons for both patient and provider reporting of ADEs, resulting in concerns of over- and underreporting. Patients are the primary information source to measure symptoms. Physicians may especially underestimate those symptoms that patients are reluctant to report to or those that are less visible.[5,38] However, underestimation by physicians is not restricted to problems that may be intimate and uncomfortable to discuss, such as erectile dysfunction or incontinence, or that are more subjective, such as fatigue. It has also been observed for other symptoms, such as pain or nausea.[12,15,33] We also observed this for symptoms that can be easily queried, such as abdominal pain, dyspepsia and constipation. That these ADEs are underreported can be due to reluctance of both providers and patients to communicate about possible ADEs.[5] For specific types of symptomatic ADEs, which can be supported by laboratory measurements, the results may thus be different. In our study, provider-based methods seemed to overestimate lactic acidosis and hypoglycaemia in comparison with the rates mentioned in the SPC. It is likely that this was partly driven by laboratory results as an additional source of information or confirmation for the provider-based ADE measurements. Several other explanations have been suggested as to why provider-oriented methods lead to lower estimates of symptomatic ADEs than patient-oriented methods.[4,5] Providers may undervalue or be sceptical about adverse events reported by patients.[39] Furthermore, they may not document or report ADEs that they think are not that serious or that do not require further action.[35] This might explain why some ADEs were not observed at all, such as taste changes or loss of appetite for metformin or stomach pain for acarbose.

The method for reporting may introduce additional bias. Passive, open-ended reports are known to capture fewer problems than proactive screening and symptom checklists.[40-42] The prospective studies with provider-oriented methods we included used open-ended reports.[27,32] The study on patient-reported GI ADEs used a symptom checklist,[28] which can thus have led to higher estimates. Retrospective studies using provider-oriented methods often rely on medical record review. Such reviews are expected to lead to underestimations when ADEs are poorly documented. It seems that providers do not document symptoms or possible ADEs adequately in the medical records,[37,43,44] which can be due to the limitations of the documentation system. The International Classification of Primary Care coding system, for example, only provides a general code for 'adverse effect medical agent'. This implies that assessing specific ADEs using medical records needs to rely on related reporting of a symptom or diagnosis that may be difficult to distinguish as an ADE. This can explain why ADE rates found with medical record review can also be lower than provider-based rates reported in clinical trials.[24] In contrast to most observational studies, trials rely on more specific, prospective monitoring. Only one of our included studies conducted prospective monitoring using case report forms.[32]

Unfortunately, this study only presented the rate for hypoglycaemia in patients receiving acarbose monotherapy.

We made comparisons for studies focusing on the same drug, ADE and duration of ADE measurement. There were, however, differences in the patient populations. For our comparison of GI ADEs measured in studies of metformin, the studies with provider-oriented methods included patients who were initial users and partly had a higher risk for developing ADEs, whereas the study with the patient-reported method included a general patient population of prevalent users. Given these differences, one can expect that provider-based rates would have been lower in a non-restricted population of prevalent users. The study with patient-reported ADEs, on the other hand, was slightly confounded by concomitant use of sulfonylurea drugs, which may lead to overestimations.[28] In this study, ADE rates were reported separately for patients using sulfonylurea drugs, showing lower rates for all ADEs except constipation.[28] This confounding by concomitant use could thus explain why the rate for constipation was relatively high in this study.

We focused on observational studies, since we were interested in comparing methods for measuring the safety profile of drugs in everyday practice. None of the studies mentioned any causality assessment. The ADEs reported, however, could all be caused by the drugs studied. We compared the ADE rates with those mentioned in the SPC. The SPC reports crude rates of adverse events with at least a suspected causal relationship. If the choice of the frequency category is based on different studies, the category representing the highest frequency should be chosen. Various study designs can be used for these SPC rates, but usually the data come from clinical trials. In such trials, adverse event data can be either collected through the healthcare provider or elicited directly from patients. In clinical trials, however, the ADE rates may be lower than in everyday clinical practice because of the inclusion of a more restricted, healthier or younger patient population.[45] Since there is no gold standard for the 'true' ADE rate of a drug, we employed the SPC as the available recognized reference.

A major limitation of the current analysis is the small number of included studies, especially using patient-oriented methods for measurement of ADEs other than hypoglycaemia. The only study we could use for agreement and validity assessment included a small percentage of patients receiving combination therapy. Therefore, we cannot draw firm conclusions regarding the value of patient-oriented methods. Furthermore, we limited our study to oral blood glucose-lowering drugs. For other drugs, with different usage patterns and safety profiles, the results might be different. An important reason that our comparison was mainly restricted to metformin is that other oral blood glucose-lowering drugs are often co-prescribed or have been studied at class level. Since the safety profile as reported in the SPC of, for example, sulfonylurea drugs or thiazolidinediones, is not identical at class level, we could not include these studies.

Conclusions

To ensure meaningful information on the safety profile of a drug, regulatory guidelines should specify how to measure ADEs in trials and postmarketing studies. Our study is a first attempt to assess the concurrent validity of different methods for quantifying ADEs in the field of diabetes. Our findings add to the body of knowledge from other fields that provider-oriented methods are too limited and are likely to underestimate such ADE rates. More proactive examination and questioning of patients, and better documentation of ADEs, could improve provider-oriented methods. Since there seems to be no clear overreporting by patients, patients can be considered as a valuable direct source to get better estimates of symptomatic ADE rates.

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