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Adverse drug reaction monitoring of newer oral anti-diabetic drugs – A pharmacovigilance perspective

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Abstract

Objective: To monitor and evaluate adverse drug reactions (ADRs) of newer oral anti-diabetic drugs in type II diabetics by spontaneous/solicited ADR monitoring.

Material and methods: Two hundred and thirty two diabetic patients on newer oral antidiabetic drugs were evaluated prospectively in a cross-sectional study over a period of eighteen months. All patients were followed up for ADRs which were evaluated for incidence, frequency, severity and causality. ADR severity was graded according to University of Virginia Health System Adverse Drug Reaction Reporting program criteria and causality assessment was done using WHO-UMC scale.

Results: 190 out of 232 patients (42 patients lost to follow up) were evaluated. ADRs were observed in 34 cases (17.9%). Most common ADRs were gastrointestinal (44.2%) followed by musculoskeletal (17.6%), metabolic (14.7%), infections (5.9%) and others (17.6%). The maximal frequency of ADRs was seen with sitagliptin (6.4%) followed by vildagliptin(3.8%), saxagliptin(2.7%), saroglitazar(2.1%), linagliptin(1.6%), canagliflozin(1.6%). 25(73.5%), 8(23.5%) and 1(3%) ADRs were mild, moderate and severe respectively. 24(70%) ADRs were classified as possible, 9(27%) probable and 1(3%) unlikely on causality assessment.

Conclusion: Newer oral antidiabetic drugs like gliptins and SGLT-2 inhibitors have potential to cause ADRs. Gastro-intestinal, musculoskeletal, metabolic were most common ADRs. Active pharmacovigilance should be carried out for risk identification and management.

Keywords: Pharmacovigilance, Diabetes, Adverse dug reaction

1. Introduction

Diabetes mellitus (DM) is a syndrome with disordered metabolism and inappropriate hyperglycemia due to either a deficiency of insulin secretion or a combination of insulin resistance and inadequate insulin secretion.[1] Type 2 diabetes is the more common form and accounts for more than 90 per cent of all diabetes cases.[2] The World Health Organization (WHO), considers T2DM as an apparent epidemic which is especially increasing at an alarming rate in developing countries.[2]

Pharmacological treatment remains the main option for most of these patients. The conventional options for type 2 diabetes mellitus include drugs that have been relatively long on the market such as biguanides, sulfonylureas, alpha-glucosidase inhibitors, meglitinides and thiazolidinedione.

In spite of efficacy in achieving glycemic control, there are some safety issues with conventional antidiabetic drugs. Therefore, the medications must be individualized for each patient by balancing the potential for lowering HbA1c and anticipated long-term benefit with specific safety issues, as well as other characteristics of regimens, including side effects, tolerability, ease of use, long-term adherence, expense and the nonglycemic effects of the medications.

Apart from the conventional oral hypoglycaemic drugs which have been in the market for a long time, there are a number of new drugs that have been introduced during the last decade. Among the recently approved anti-diabetic drugs are DPP-IV inhibitors- sitagliptin, vildagliptin, linagliptin, saxagliptin, alogliptin; PPAR- α/γ agonist- saroglitazar; SGLT-2 inhibitors- canagliflozin, dapagliflozin. All of these except alogliptin are available in India.

DPP-IV inhibitor is a new class of oral antidiabetic drugs which by inhibiting the degradation of incretins: glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) improve fasting and postprandial hyperglycemia. The first dipeptidyl peptidase-4 (DPP-IV) inhibitor- sitagliptin was approved in 2006.[3]

Saroglitazar is a novel first in class drug and is the first indigenously developed new clinical entity in India. It is a dual PPAR α/γ agonist with particular benefit in patients with diabetic dyslipidaemia. Literature review has shown good efficacy and acceptable safety profile.[4]

Sodium glucose cotransporter-2 (SGLT-2) inhibitors are a new class of glucose-lowering agents that reduce hyperglycaemia in patients with T2DM by reducing renal glucose reabsorption, as a result, they increase urinary glucose excretion. The available data for SGLT-2 inhibitors: canagliflozin and dapagliflozin, suggests a good tolerability profile. The most frequently reported adverse events with these are female genital mycotic infections, urinary tract infections and increased urination.[5]

Owing to the fact that the newer oral anti-diabetic drugs have been in the market for last few years only, the data regarding their safety is limited particularly in Indian population. Therefore, the detection of adverse drug reactions (ADRs) through pharmacovigilance has become increasingly significant. Hence, the present study is planned to actively generate data on the safety profile of currently prescribed newer oral anti-diabetic drugs in diabetic Indian population by doing monitoring of ADRs.

2. Material and Methods

2.1 Study design

The study was conducted in a cross-sectional manner and involved spontaneous and solicited pharmacovigilance monitoring of currently prescribed newer oral anti-diabetic drugs. The study was conducted by the Department of Pharmacology, Pt. B.D. Sharma PGIMS, Rohtak (Haryana). The study was conducted in 230 patients for duration of 12 months. Study was conducted in accordance with the principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

2.2 Study sample and eligibility

The patients diagnosed with Type 2 diabetes attending endocrinology outpatient clinic of Pt. B.D. Sharma PGIMS, Rohtak and on treatment with at least one newer oral anti-diabetic drug were screened for possible inclusion in the study. They were screened with the help of a predefined inclusion and exclusion criteria for the study. The drugs which are relatively new and have been in the market for around 5-7 years were taken as new drug. These include specifically the following drugs: DPP-IV inhibitors: gliptins - sitagliptin, vildagliptin, saxagliptin, linagliptin, and their combinations with metformin, PPAR α/γ agonist: saroglitazar. SGLT-2 inhibitors: canagliflozin, dapagliflozin were introduced in the market later on and hence included subsequently during the course of the study. All patients were asked to follow up at monthly interval and whenever they develop any side effect. They were screened clinically and investigated suitably for any ADRs.

2.3 Selection criteria

2.3.1 Inclusion criteria

1. Patients of >18 yrs age of either sex diagnosed to have Type 2 diabetes.
2. Patients with T2DM currently were taking at least one newer oral anti-diabetic drug.

2.3.2 Exclusion criteria

1. Diabetic patients not taking the newer oral anti-diabetic drugs.
2. Newly diagnosed naive diabetic patients.

2.4 Study conduct

2.4.1 Adverse event (AE) monitoring

Adverse event monitoring was carried out by Spontaneous/ Solicited reporting. The patient's data including the demographic, clinical & biochemical details was entered into patient's case record form (CRF). The Central Drugs Standard Control Organisation (CDSCO) proforma was used and filled as and when AE was reported. The details regarding the ADR was filled in the CDSCO ADR proforma and subsequently uploaded in the WHO-UMC using the Vigiflow software. The CDSCO ADR proforma is divided into 4 parts i.e. A- Patient information, B- Suspected Adverse reaction, C- Suspected medication and D- Information about the Reporter.

2.4.2 ADR Severity:

The severity of the adverse drug reactions was graded according to the University of Virginia Health System Adverse Drug Reaction Reporting program criteria as "mild": a reaction that does not require treatment or prolongation of the hospital stay; "moderate": a reaction that requires treatment and/or a prolonged hospitalization by at least one day and "severe": a reaction that is potentially life-threatening or that which contributes to the death of the patient, that which is permanently disabling, that which requires intensive medical care (including extended hospitalization), or that which result in a congenital anomaly, cancer. [6]

2.4.3 Causality Assessment of ADRs

In the present study, WHO-UMC Scale[**7**] and Naranjo Scale [**7**] were used to analyse the causality assessment between the drug and suspected reaction.

WHO-UMC Scale: The ADRs are categorised according to certain criteria: time relationship to drug intake, any alternative medications taken, response to withdrawal and response on re-introduction of the drug. Depending on these

criteria the ADRs are classified as Certain, Probable, Possible and Unlikely.

Naranjo Scale: According to Naranjo Criteria, the ADRs are analysed on the basis of a questionnaire comprising 10 questions in which each question is given a score of +2, +1, 0 or -1 depending on the analysis. When totalled if the score is >9 – labelled as definite ADR, if 5-8 – probable ADR, if 1-4 – possible ADR, if 0 – doubtful ADR.

2.5 Preventability Assessment:

Preventability of ADRs were assessed by modified Schumock and Thornton criteria[10], which comprises of three sections namely definitely preventable, probably preventable and not preventable. ADRs are categorised as:

- "definitely preventable" if (a) there is history of allergy or previous reactions to the drug (b) inappropriate drug for the patient's clinical condition (c) dose, route or frequency of administration inappropriate for the patient's age, weight or disease state (d) toxic serum drug concentration (or laboratory monitoring test) documented (e) a known treatment for the Adverse Drug Reaction exists.
- "probably preventable" if (a) required therapeutic drug monitoring or other necessary laboratory tests not performed (b) drug interaction involved in the ADR (c) poor compliance involved in the ADR (d) preventive measures not prescribed or administered to the patient. Any answer of "yes" to any question suggests that the ADR might have been preventable.
- If none of the above criteria is fulfilled, then it was classified as "not preventable".

3. Results

A total of 264 newer oral antidiabetics were prescribed in the 230 patients followed up for the study. ADRs were coded according to the Adverse Reaction Terminology (WHO-ART) and Medical Dictionary for Regulatory Activities in which terms for specific adverse events that are alike or pertain to the same organ system is categorized by System Organ Class (SOC). Table 1 shows the demographic profile of the patients recruited for the study.

Table 1: Demographic profile of the patients on newer OHAs

	Parameter	Group	Total no. of patients (n=230)	
			N	%
1	Age	21-30 years	9	4
		31-40 years	29	12.6
		41-50 years	60	26
		51-60 years	85	37
		61-70 years	40	17.4
		>70 years	7	3
2	Gender	Male	118	51
		Female	112	49
3	Duration of T2DM	<5 years	68	29.5
		5-10 years	84	36.5
		11-20 years	67	29.2
		>20 years	11	4.8
4	Co-morbid conditions	Hypertension	78	34.7
		CAD	17	7.1
		Hypothyroidism	23	8.5
		Osteoporosis	17	7.1
		BHP	6	2.6
		PAD	2	0.9
5	Drug category	Sitagliptin	86	37.4
		Vildagliptin	54	23.5
		Linagliptin	15	6.5
		Saxagliptin	49	21.3
		Saroglitazar	20	8.7
		Canagliflozin	20	8.7
		Dapagliflozin	20	8.7
6	No. of newer OHAs taken	1	197	85.6
		2	32	14
		3	1	0.4
7	Concomitant other anti-diabetic drugs			
	a) Older OHAs		118	50.7
	b) Insulin		25	9.1

The classification of all the ADRs into different system organ class (SOC) involved was done according to the WHO-ART classification. The ADRs were categorized into gastro-intestinal system disorders, musculoskeletal disorders, metabolic disorders, CNS disorders, genito-urinary disorders and few ADRs were categorized as "others" which could not

be classified under any SOC. Gastro-intestinal system disorders comprise the maximum number (43.2%) of ADRs followed by metabolic disorders (16%), CNS disorders (13.6%), musculoskeletal disorders (11.4%) and genito-urinary disorders (6.8%). 9% of ADRs which could not be classified under any SOC were 1 ADR each of CHF, URTI and 2 ADRs of fatigue. Figure 1 shows the distribution pattern of ADRs according to SOC involved. It was seen that the maximum number of ADRs due to newer oral anti-diabetic drugs (43.2%) were due to involvement of gastro-intestinal system, followed by metabolic disorders (16%), CNS disorders (13.6%), musculoskeletal disorders (11.4%). Genito-urinary disorders comprised 6.8% of total number of ADRs, whereas 9% of ADRs could not be classified under any SOC.

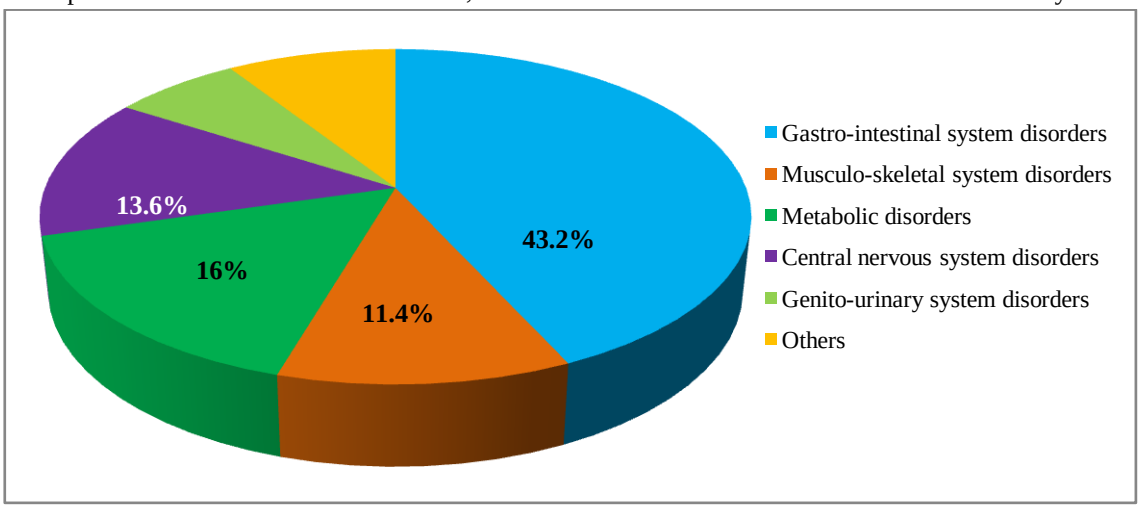

Figure 1: Distribution pattern of ADRs with different newer oral anti-diabetic drugs as per System Organ Class (SOC)

Table 2: ADR quantum with different classes of newer oral anti-diabetic drugs according to different system organ class (SOC) involved

SOC involved	ADR	DPP-IV inhibitors (204)	PPAR-γ agonist (20)	SGLT-2 inhibitors (40)	Total
GI system disorders	Dyspepsia	7	-	-	19 (43.2%)
	Diarrhoea	5	-	1	
	Constipation	2	-	-	
	Flatulence	2	-	-	
	Abdominal pain	1	-	-	
	Gastritis	0	1	-	
Musculoskeletal disorders	Myalgia	3	-	-	5 (11.4%)
	Joint pain	2	-	-	
Metabolic disorders	Hypoglycaemia	5	-	2	7 (16%)
CNS disorders	Headache	4	-	-	6 (13.6%)
	Dizziness	1	-	1	
Genito-urinary disorders	Pus cells in urine	0	-	1	3 (6.8%)
	Increased frequency of urination	0	-	2	
Others	CHF	1	-	-	4 (9%)
	URTI	1	-	-	
	Fatigue	1	1	-	
Total		35 (17.16%)	2 (10%)	7 (17.5%)	44 (100%)

Table 2 show the pattern of ADRs categorized according to different system organ class (SOC) involved. A total of 44 ADRs were reported among 230 type 2 diabetic patients who were on 264 newer oral anti-diabetic drugs. It was seen that the maximum number of ADRs (43.2%) were due to involvement of gastro-intestinal system.

3.1 Serious adverse reaction:

Seriousness of ADRs was evaluated as per criteria in CDSCO ADR proforma. Out of 44 ADRs reported with various groups of newer oral anti-diabetic drugs, 1 ADR was classified as serious, and remaining 43 ADRs were categorized as non-serious.

3.2 Severity assessment of ADRs:

Table 3 shows the severity assessment of ADRs with different classes of newer oral anti-diabetic drugs, graded

according to the University of Virginia Health System Adverse Drug Reaction Reporting program criteria. Out of 35 ADRs reported with DPP-IV inhibitors, 16 ADRs were mild, 18 ADRs were moderate and 1 ADR was categorized as severe. Severity assessment done for 2 ADRs reported with PPAR- γ agonist showed 1 ADR as mild and 1 ADR as moderate; whereas with SGLT-2 inhibitors, 4 ADRs were mild, 3 ADRs were moderate and none were severe. There was no withdrawal from treatment due to ADR in any patient.

Table 3: Severity assessment of ADRs with different classes of newer oral anti-diabetic drugs

	DPP-IV inhibitors (204)	PPAR-γ agonist (20)	SGLT-2 inhibitors (40)
Mild	16	1	4
Moderate	18	1	3
Severe	1	0	0
Total	35	2	7

3.3 Causality assessment of ADRs

Causality assessment of ADRs with different classes of newer oral anti-diabetic drugs were done according to two different scales i.e. WHO-UMC scale and Naranjo scale.

3.4 Causality assessment of ADRs according to WHO-UMC scale

Causality assessment of ADRs was done using WHO-UMC scale which categorises ADRs as "certain", "probable", "possible" and "ünlikely". Table 4 shows that out of 35 ADRs reported with DPP-IV inhibitors, 11 ADRs were classified as probable and 24 ADRs as possible, whereas none could be categorized as certain or unlikely. Similarly, 2 ADRs reported with PPAR-γ agonist and both were categorized as possible. With regard to SGLT-2 inhibitors, it was seen that all 7 ADRs were categorized as possible and none were certain, probable or unlikely. Overall, out of 44 ADRs, 11 ADRs were categorized as probable and 33 ADRs were possible.

Table 4: Causality assessment of ADRs with different classes of newer oral anti-diabetic drugs according to WHO-UMC scale

Newer OHAs	Certain	Probable	Possible	Unlikely
DPP-IV inhibitors (204)	0	11	24	0
PPAR-γ agonist (20)	0	0	2	0
SGLT-2 inhibitors (40)	0	0	7	0
Total	0	11	33	0

3.5 Causality assessment of ADRs according to Naranjo scale:

The causality assessments of ADRs were also done according to Naranjo scale which categorises ADRs as "certain", "probable", "possible" and "unlikely". Table 5 shows causality assessment of ADRs with different classes of newer oral anti-diabetic drugs according to Naranjo scale. It is seen that out of 35 ADRs reported with DPP-IV inhibitors, 11 ADRs were classified as probable and 24 ADRs as possible, whereas none could be categorized as certain or unlikely. Similarly, 2 ADRs reported with PPAR-γ agonist and both were categorized as possible. With regard to SGLT-2 inhibitors, it was seen that all 7 ADRs were categorized as possible and none were certain, probable or unlikely. Overall, out of 44 ADRs, 11 ADRs were categorized as probable and 33 ADRs were possible.

Table 5: Causality assessment of ADRs with different classes of newer oral anti-diabetic drugs according to Naranjo scale

Newer OHAs	Certain	Probable	Possible	Unlikely
DPP-IV inhibitors (204)	0	13	22	0
PPAR-γ agonist (20)	0	0	2	0
SGLT-2 inhibitors (40)	0	0	7	0
Total	0	13	31	0

ADRs that were categorized as "probable", were 11 according to WHO-UMC scale and 13 according to Naranjo scale. Whereas ADRs that were categorized as "possible" were 33 using WHO-UMC scale and 31 according to Naranjo scale.

3.6 Preventability of ADRs

Table 6 shows the preventability assessment of ADRs with different classes of newer oral anti-diabetic drugs were assessed and categorized using modified Schumock and Thornton criteria. Out of 35 ADRs reported with DPP-IV inhibitors, 16 ADRs were categorized as probably preventable and 19 ADRs were not preventable, whereas none were definitely preventable. With regards to PPAR- γ agonist, out of 2 reported ADRs, 1 ADR was classified as probably preventable and 1 ADR as not preventable; whereas with SGLT-2 inhibitors, 2 ADRs were probably preventable, 5 ADRs were not preventable and none could be classified as definitely preventable.

Table 6: Preventability assessment of ADRs with different classes of newer oral anti-diabetic drugs

Preventability	DPP-IV inhibitors (204)	PPAR-γ agonist (20)	SGLT-2 inhibitors (40)
Definitely preventable	0	0	0
Probably preventable	16	1	2
Not preventable	19	1	5
Total	35	2	7

4. Discussion

A number of newer oral anti-diabetic drugs have been introduced in the market for last few years; the data regarding their safety is limited, particularly in Indian population. Hence, the present study was planned to actively generate data on the safety profile of currently prescribed newer oral anti-diabetic drugs among type 2 diabetic patients by spontaneous/solicited ADR monitoring.

A total of 230 patients diagnosed with type 2 diabetes, attending the endocrinology OPD at Pt. B.D. Sharma PGIMS, Rohtak and on treatment with at least one newer oral anti-diabetic drug were followed up. A total of 264 newer oral antidiabetic drugs were prescribed in 230 type 2 diabetic patients who were followed up for any ADR in the study. Any spontaneous reports of ADRs were also included for evaluation.

4.1 Analysis of ADRs with newer oral antidiabetic drugs:

a)According to number of ADRs: In the current study, out of 204 patients on DPP-IV inhibitors, ADRs were reported in 17.1%. Kajiwara *et al*[10] evaluated safety profile of DPP-IV inhibitors in 1550 patients and reported an incidence of 5.9% ADRs.

As regards with 20 patients on PPAR- α/γ agonist: saroglitazar, ADRs were reported in 10%. The incidence of ADRs with saroglitazar in the present study was in accordance with a similar study by Chatterjee *et al* [11] which demonstrated 11.8% of ADRs with saroglitazar.

Amongst 40 patients on SGLT-2 inhibitors: canagliflozin and dapagliflozin, ADRs were reported in 17.5% patients.

b)According to involvement of SOC:

In the current study, ADRs were analyzed by stratification according to system organ class (SOC) following WHO-ART classification.

4.2 Safety assessment of DPP-IV inhibitors:

In the present study, out of 204 type 2 diabetic patients on DPP-IV inhibitors, 39.7% (81) were on monotherapy and 60.3% (123) patients were on FDC of the drug.

i) Gastro-intestinal system ADRs: Out of 35 ADRs reported due to DPP-IV inhibitors, it was seen that gastro-intestinal system disorders constituted the maximum number (48.6%) followed by musculoskeletal, metabolic and CNS disorders which constituted 14.3% each. A study by Kajiwara *et al*[10] also showed that the maximum number of ADRs with DPP-IV inhibitors was on GI system which is on similar pattern with present study.

Out of 17 GI related ADRs due to DPP-IV inhibitors, 4 (23.5%) were due to monotherapy and remaining 13 (76.5%) were seen in patients taking FDC of the drug. Amongst all the different DPP-IV inhibitors, the maximum GI involvement (58.9%) was seen due to FDC of sitagliptin with metformin. The incidences of dyspepsia and diarrhoea constituted the maximum number of ADRs due to GI involvement by DPP-IV inhibitors. Most of the ADRs were usually mild and either subsided with time or on dose reduction.

The present study showed that GI side effects were observed in 14.7% of patients on FDC of sitagliptin. This is in accordance with the results from study by Reasner *et al* [12], which showed that gastrointestinal side effects were observed in 20.6% of patients on FDC of sitagliptin and 24.6% patients on metformin monotherapy.

A similar study by Herman *et al* [13] assessed the incidence of GI adverse effects with sitagliptin vis-à-vis with sitagliptin combination therapy and different doses of metformin. The incidences of gastrointestinal adverse effects were found to be generally lower in the sitagliptin group and similar between the metformin monotherapy and combination groups. The results were consistent with that of the present study where the maximum incidence of GI related ADRs were seen with FDC of sitagliptin. Overall in the present study, the GI system ADRs were mild and subsided with symptomatic treatment or with time on continued treatment.

This is further affirmed by Wainstein *et al* [14] who showed that there were numerically more adverse effects with sitagliptin and metformin FDC, mainly from a significantly higher incidence of gastrointestinal side effects including, diarrhea, nausea, vomiting, and abdominal pain/discomfort when compared with conventional OHAs (25.6% with sita/met FDC and 14.3% with pioglitazone).

Therefore, the results of the previous studies indicate that sitagliptin when used alone was not associated with increased risk for diarrhea, nausea or vomiting as compared to placebo and combination of sitagliptin and metformin

therapy marginally increases the gastrointestinal side effects compared to conventional OHAs. Thus, sitagliptin monotherapy treatment appeared to have generally better gastrointestinal tolerability relative to treatment with metformin monotherapy or combination treatments with metformin and other conventional OHAs. The results of the present study in this regard match with these studies.

Out of 54 patients on vildagliptin, ADRs were reported in 6 patients (11%). Of all ADRs with vildagliptin, gastro-intestinal system disorders constituted the maximum number (50%), out of which 1 ADR was due to vildagliptin monotherapy and 2 ADRs were reported with patients on vildagliptin and metformin combination therapy.

In a Korean study [15] to assess the safety of vildagliptin versus sulfonylureas, it was seen that vildagliptin metformin combination was associated with a significant number of GI related side effects such as metallic taste, reduced appetite or dyspepsia. These ADRs were attributed to metformin rather than vildagliptin, since metformin has been known to be associated with increased incidence of gastrointestinal adverse events compared with other antidiabetic agents and the GI side effects in the patients disappeared after vildagliptin monotherapy. The results of present study are consistent with this study, where GI ADRs were mild and either resolved over time or with dose reduction. None required drug discontinuation.

As regards with saxagliptin, out of 7 reported ADRs, 3 were attributed due to involvement of GI system: 2 ADRs with monotherapy and 1 due to FDC of the drug with metformin.

In a study by De Fronzo *et al* [16] which assessed the safety of saxagliptin as add-on therapy in type 2 diabetic patients, it was seen that incidence of adverse events related to gastrointestinal disorders was similar in patients treated with saxagliptin (23.0%) versus placebo plus metformin (24.0%) and saxagliptin was not associated with an increased incidence of gastrointestinal disorders as compared to placebo.

No gastro-intestinal system ADR was reported in the present study due to linagliptin with 15 prescriptions.

ii) Metabolic disorders: In the present study, 5 ADRs of metabolic disorders i.e. hypoglycaemia were reported amongst 204 patients on DPP-IV inhibitors: 1 ADR due to monotherapy and 4 due to FDC of DPP-IV inhibitors with metformin. These patients were on concomitant treatment with conventional OHAs. No episode of hypoglycemia exhibited marked severity i.e. loss of consciousness or immediate requirement for medical assistance.

These findings are in accordance with those of the study conducted by Goossen and Graber [17] who observed that hypoglycemic risk was similar to placebo when a DPP-IV inhibitor was used as monotherapy or as combination therapy with metformin. However, they also re-affirmed that the incidence of hypoglycemia was increased when patients with background treatment with insulin or a sulfonylurea were treated with sitagliptin, saxagliptin or linagliptin. Overall, studies show a low risk of hypoglycaemia during treatment with DPP-IV inhibitors which is mild and does not mandate a discontinuation of treatment.

iii) Musculoskeletal system disorders: In the present study, 14.3% of ADRs with DPP-IV inhibitors were due to involvement of musculoskeletal system. There were 3 ADRs of myalgia and 2 of joint pain. Both myalgia and joint pain was mild and subsided in due course of time and did not lead to treatment discontinuation. Tarapues *et al* [18] reported that musculoskeletal disorders are adverse reactions often associated with gliptins that despite not being serious, may impair the treatment adherence in patients with type 2 diabetes. Analysis of literature did not reveal any possible explanation of the association of musculoskeletal disorder and gliptins.

iv) CNS disorders: In the present study, 14.3% of ADRs with DPP-IV inhibitors were due to involvement of CNS. There were 4 ADRs of headache and 1 of dizziness. Goossen and Graeber [17] have also reported that treatment with DPP-IV inhibitors was associated with a slightly elevated risk (relative risk: 1.14) for nervous system disorders, mainly dizziness and headache in comparison to placebo and showed that the risk was not increased compared to other antidiabetic drugs. In the present study, out of 4 ADRs of headache, 2 were caused due to sitagliptin.

In the present study, one ADR each of headache with saxagliptin and linagliptin was reported. Although there is no conclusive evidence of significant association of headache with saxagliptin and linagliptin intake, but as quoted earlier, a study by Goossen and Graeber [18] have reported that treatment with DPP-IV inhibitors was associated with a slightly elevated risk of headache. FDA reports of ADRs of headache with linagliptin and saxagliptin confirms this.

v) Others: There was one ADR of nasopharyngitis reported by a patient on FDC of sitagliptin with metformin. In controlled clinical studies of both monotherapy and combination therapy of sitagliptin, nasopharyngitis was one of the most commonly reported ADR. Goossen and Graeber [18] have also noted the same trend. The risk of nasopharyngitis was found to be marginally elevated in a meta-analysis of 34 gliptin trials (Relative Risk: RR 1.13) where statistical significance was seen only in the sitagliptin subgroup (RR 1.35).

It is hypothesized that the effect of DPP-IV inhibitors results in a slight imbalance of the immune system that causes an increased risk of common, less severe infections such as (viral) upper respiratory infections. This is supported by the results of the pivotal randomized clinical trials that also reported increased numbers of common infections rather than serious infections.

One case of CHF was reported in a patient of coronary heart disease on sitagliptin monotherapy for whom drug discontinuation was done. However in a study by Read *et al* [19] it was demonstrated that in diabetic patients who also suffer from coronary heart disease, treatment with sitagliptin improved their heart function and coronary artery perfusion, as observed in echo-dobutamine tests.

This was further asserted by Eurich *et al* [20] in a retrospective population based cohort study of approximately 72,740 newly treated patients with type 2 diabetes, that use of sitagliptin was not associated with an increased risk of cardiovascular-related hospital admissions or deaths in comparison with other antidiabetic drugs. Further studies are required to analyse the effect of sitagliptin on cardiovascular outcomes.

There was one ADR of fatigue with FDC of vildagliptin and metformin. Literature review did not reveal any possible association of fatigue in patients prescribed on vildagliptin.

4.3 Causality assessment of ADRs with DPP-IV inhibitors:

When causality assessment of 35 ADRs due to DPP-IV inhibitors was done according to WHO-UMC scale, 11 ADRs were categorized as probable and 24 as possible. Whereas according to Naranjo assessment scale, 13 ADRs were probable and 22 ADRs were possible. Out of ADRs which were classified as probable, only a dose reduction was done.

4.4 Severity assessment of ADRs with DPP-IV inhibitors:

When ADRs were assessed for severity according to University of Virginia Health System Adverse Drug Reaction Reporting program criteria, 16 ADRs were classified mild, 18 ADRs as moderate and 1 ADR as severe.

4.5 Preventability assessment of ADRs with DPP-IV inhibitors:

With regards to preventability of ADRs, assessed using modified Schumock and Thornton criteria, 16 ADRs were classified as probably preventable, 19 ADRs as not preventable and none could be classified as definitely preventable.

Overall, DPP-IV inhibitors appear to have a good safety profile for patients with type 2 diabetes. However, close pharmacovigilance is necessary to further confirm the association of drugs and ADRs. To address the uncertainty regarding their potential impact on cardiovascular outcomes further long-term studies are required.

4.6 Safety assessment of PPAR α/γ agonist:

In the present study, out of 20 patients on saroglitazar, adverse drug reactions were noted in 2 patients (10%). There was one ADR each of gastritis and fatigue. PRESS V (Prospective Randomized Efficacy and Safety of Saroglitazar V) [21] also showed incidences of similar ADRs. It was the first prospective confirmatory clinical study of saroglitazar in diabetic dyslipidemia. In another multicenter study to evaluate the efficacy and safety of different doses of saroglitazar versus placebo (PRESS VI) [22]**,** gastritis was reported to be most common adverse effect. These studies did not provide any possible explanation of association of gastritis or fatigue with saroglitazar use but reported that the ADRs due to saroglitazar were mild to moderate in intensity. Our findings are in agreement with these studies.

4.7 Causality, severity and preventability assessment of ADRs with PPAR-α/γ agonist: Causality assessment on both WHO-UMC scale and Naranjo scale categorized both ADRs as possible. 1 ADR was mild and 1 ADR was moderate on severity scale. None required drug discontinuation or dose reduction. With regards to preventability of ADRs assessed using modified Schumock and Thornton criteria, 1 ADR was classified as probably preventable and the other as not preventable.

Saroglitazar seems to be safe and well tolerated in management of diabetic dyslipidaemia. Long-term phase 4 study (PRESS X) of saroglitazar are ongoing to further elucidate its efficacy and safety in dyslipidemic diabetic patients.

4.8 Safety assessment of SGLT-2 inhibitors:

Amongst 40 patients on SGLT-2 inhibitors: canagliflozin and dapagliflozin, adverse drug reaction monitoring documented 7 ADRs (17.5%). Genito-urinary system disorders (7.5%) and hypoglycaemia (5%) comprised the major chunk of ADRs. Genital mycotic infections and urinary tract infections have been the most commonly reported adverse events associated with SGLT-2 inhibition to date. A 2013 meta-analysis [23] furthers confirms this which states that when compared to other anti-diabetes agents, urinary tract infections were more common with SGLT2 inhibitors (odds ratio, 1.42 [95% CI 1.06, 1.90]), as were genital tract infections. These occurrences are usually mild to moderate and responsive to treatment and they rarely result in discontinuation of therapy. It appears logical that glucosuria, deliberately induced by SGLT2 inhibition, favours urinary tract infections, as glucose serves as nutrient for bacteria.

In our study, there were 2 ADRs of hypoglycaemia due to canagliflozin. Wilding *et al* [24] documented that mild hypoglycemia occurs with concurrent use of SGLT-2 inhibitors and insulin or insulin secretagogues. But there is a low risk of hypoglycemia among subjects treated with canagliflozin taken as monotherapy or in combination with other anti-hyperglycemic agents not associated with hypoglycemia. Hence, reductions in the dosages of such agents are recommended when used in conjunction with SGLT-2 inhibitors. Dapagliflozin has a low intrinsic propensity to cause hypoglycemia. However, hypoglycemic events were more frequent when dapagliflozin was added to insulin or SU therapy.

There was one reported ADR of dizziness due to dapagliflozin which may be attributed to volume depletion effect and resulting hypotension. It is seen that hypotension occurred more frequently in dapagliflozin-treated groups than

placebo groups for subjects who were elderly, had moderate renal impairment or were treated with loop diuretics.

4.9 Causality, severity and preventability assessment of ADRs with SGLT-2 inhibitors:

Causality assessment using both WHO-UMC scale and Naranjo scale categorized all 7 ADRs as possible. 4 ADRs were mild, 3 moderate and none severe on the severity scale. With regards to preventability of ADRs, 2 ADRs was classified as probably preventable and 5 as not preventable.

Thus, SGLT-2 inhibitors are generally well tolerated. But, relatively high incidence of genital infections and UTIs mandate that the patients should be monitored for these. They should be informed regarding the signs and symptoms of these infections and the need to seek treatment should they occur. Taken together, these results suggest that SGLT-2 inhibitors represent a valuable therapeutic option for the management of patients with type 2 diabetes.

Overall, the newer oral anti-diabetic drugs appear to be a safe option for patients with type 2 diabetes. However, close pharmacovigilance is necessary to address the uncertainty regarding the ADRs, while their potential impact on long term ADRs like cardiovascular involvement should be further elucidated after completion of more long-term studies.

5. Conclusion

Overall, newer oral antidiabetic drugs like gliptins and SGLT-2 inhibitors appear to have a good safety profile, but they also have potential to cause ADRs. Gastro-intestinal, musculoskeletal, metabolic disorders were most common ADRs. As the newer drugs are increasingly being prescribed in Indian scenario, hence the need for ADR monitoring is growing than ever before. Therefore, active pharmacovigilance should be carried out for risk identification and management. It is also important to motivate healthcare providers to understand their role and responsibility in the detection, management, documentation, and reporting of ADRs for optimizing patient safety.

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