DOI: 10.7860/JCDR/2025/74419.20834

Original Article

Pharmacology Section

Evaluation of Oral Antidiabetes Drugs in Patients of Uncontrolled Type 2 Diabetes Mellitus: A Cohort Study

SAMIKSHA J SONAR[1], VISHAL MISHRA[2], ANURADHA M GANDHI[3], PRAKRUTI P PATEL[4], CHETNA K DESAI[5]

ABSTRACT

Introduction: The prevalence of uncontrolled Type 2 Diabetes Mellitus (T2DM) is higher due to non compliance to non pharmacological measures or pharmacotherapy, or due to disease progression, despite the availability of various oral antidiabetic drugs.

Aim: To evaluate Oral Antidiabetic Drugs (OADs) in terms of treatment outcome as well as adherence.

Materials and Methods: This was a single-centre cohort study, patients of uncontrolled T2DM on OAD(s) were enrolled for 12 months and followed-up monthly for six months. Details of blood sugar levels and antidiabetic treatment were recorded at each visit. Adherence to Antidiabetic Diet (ADD) and OAD(s) was studied using drug adherence diary, pill count method and Medication Adherence Report Scale (MARS-5) questionnaire. Data was presented in percentage, mean, standard deviation or as p-value (Z test of significance).

Results: A total with 56 patients with uncontrolled T2DM were included in the study. There were 36 (64%) female patients, and mean age group and Body Mass Index (BMI) of patients was 57.14±10.3 years and 26.4±5.53 kg/m^2, respectively. Hypertension was present in 45 (80%) of patients. There was statistically significant reduction in mean HbA1c% to 6.85±0.83% compared to the baseline. Percentage patients prescribed single OAD decreased, and that described dual OADs regimen increased during study period. At time of enrollment, a total of 29 (52%) patients were adherent to ADD, and 44 (79%) were adherent to OAD(s). By the end of the study, 49 (94%, n=52) patients were adherent to ADD, and 51 (98%, n=52) patient were adherent to OAD(s). MARS-5 assessment showed that main reason for non adherence was that patients forgot to take the medicine; Adverse Drug Reactions (ADRs) was observed in seven patients, mainly belonged to gastrointestinal system organ class.

Conclusion: Regular assessment of T2DM patients aids in monitoring of blood glucose levels and treatment modification. Increased number of OAD(s) and complexity of the regimen reduce drug adherence in the uncontrolled T2DM patients. Implementation of different tools for drug adherence evaluation in uncontrolled T2DM patients reinforces the importance of treatment adherence for better therapeutic outcome.

Keywords: Adverse drug reaction, Drug adherence, Medication report adherence scale, System organ class

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder of multiple aetiology [1]. About 90% of the DM patients worldwide suffer from T2DM [2]. DM is ninth major cause of death due to its complications. The International Diabetes Federation (IDF) estimates that there will be approximately 134.3 million diabetes patients by the year 2045. India has second largest number of diabetes patients in the world, after China. The prevalence of diabetes in urban India has increased from 2% in the 1970s to over 20% by 2021 [1,3].

Management of T2DM includes pharmacological as well as non pharmacological treatment. Metabolic targets to be achieved in a T2DM patient on treatment are Glycosylated Haemoglobin (HbA1c) <7.0%; Fasting Blood Sugar (FBS) between 4.4-7.2 mmol/L (<130 mg/dL); and Post-Prandial Blood Sugar (PP2BS) <10.0 mmol/L (<180 mg/dL) [1,4]. Treatment should be individualised, as risk factors and genetic susceptibility are different in each of the diagnosed case [4].

Healthy lifestyle alone in some cases helps to achieve metabolic targets. However, OAD(s) is/are also indicated and prescribed in many newly diagnosed cases of T2DM [1]. If individualised targets of glycaemic control are not achieved in patients on treatment, then disease is considered as uncontrolled. As per study by Anusuya GS et al., it was concluded that the prevalence of uncontrolled diabetes among known case was 65.4% [5]. Uncontrolled T2DM can cause serious medical complications, which could be acute or chronic (microvascular and macrovascular conditions), thereby increasing risk of mortality [1]. In such cases dose of prescribed medication is titrated upwards, or a newer class of drug is added to the regimen, only if the patient is compliant to medications and non pharmacological advices [4].

Uncontrolled T2DM is either due to non compliance to non pharmacological measures or pharmacotherapy, or due to progression of the disease. One of the main reasons is low adherence to medicines prescribed. Measurement of the drug or the metabolite levels is an accurate, direct method for drug adherence assessment, but it is a costly and invasive procedure. Drug adherence diary and pill count method; electronic monitoring system and self-reported measures—including questionnaires and visual analogue scales—are widely used and easy to use indirect method but are subjective and gives no evidence of ingested medication, with results affected by the recall bias [6]. Use of multiple methods for assessing adherence can help overcome the limitations of individual method [7,8].

Studies are lacking in Indian setup wherein the use of OADs in uncontrolled T2DM patients have been evaluated for the improvement in the blood sugar levels along with taking into consideration the adherence to various pharmacological and the non pharmacological measures using different tools. The present study was conducted to evaluate OADs in terms of treatment outcome as well as adherence in patients of uncontrolled T2DM.

MATERIALS AND METHODS

This cohort study was carried as a prospective follow-up study, at a single tertiary care hospital (Civil Hospital, Ahmedabad, Gujarat, India) after receiving approval from Institutional Ethics Committee (IEC)

{25/06/2021, Ref no. 161/2021}; for a duration of 18 months, from July 2021 to December 2022. Patients were enrolled for 12 months, and each patient was followed-up every month for six months. During the given duration, all patients of T2DM attending medicine Outpatient Department (OPD) were screened by the principal investigator.

Inclusion criteria: Patients more than 18 years of age, of either gender (male, female, others), who were known case of T2DM and diagnosed to be suffering from uncontrolled T2DM {FBS >130 mg/dL or PP2BS >180 mg/dL, and/or HbA1c >7%} [4] by the physician; and patients who were willing to participate and gave written informed consent were included in the study.

Exclusion criteria: T2DM patients requiring insulin and not able to read were excluded from the study.

Thus as per selection criteria, out of 142 T2DM patients screened, 56 patients of uncontrolled T2DM were enrolled in the study. The patients were assessed, diagnosed and treated by the physician. Details of the patients were recorded in a predefined and prevalidated Case Record Form (CRF) at the time of enrollment. Clinical profiles, laboratory investigations (FBS, PP2BS, HbA1c), drug treatment and ADRs if any were recorded at baseline and during each follow-up visit. BMI was evaluated to classify patient as underweight, overweight, or obese [9].

As the study period coincided with the COVID-19 infection period, patients who achieved subjectively better control for blood sugar levels on first-month follow-up visit and were compliant to the non pharmacological advices, as per the physician, were called upon at two monthly follow-up visit. So details of variable(s) for these patients were collected as per their follow-up visits. However, the principal investigator ensured that all the enrolled patients are at least available at 1st-month follow-up and the final follow-up visit.

Drug adherence was assessed using three methods: 1) MARS-5 questionnaires with reasoning [Annexure I]; 2) Drug Adherence Diary [Annexure II]; and 3) Pill Count. A Drug Adherence Diary was provided to the patient at time of enrollment to keep a record of the number of pills of the each OAD consumed by the patient as advised by physician, which was corelated to the pill count at each follow-up visit [6]. Pill count was calculated as the number of pills taken (the number of pills dispensed minus the number of pills counted). The cut-off for adherence rate using pill count method was kept 80% [10]. If adherence was >80% for an individual drug or average of overall regimen, the patient was considered adherent, else non adherent. For patients showing non adherence at more than one follow-up visit, the pill count adherence rate was taken as average of averages of adherence rate at each visit.

The MARS-5 questionnaires, to elicit self-report use of medicine, comprise of five questions concerning "forgetting," "changing dosages," "stopping," "skipping," and "using medication less than what is prescribed." Study subjects indicate the frequency ("always", "often", "sometimes", "rarely" or "never") for each question using the responses with ascending scores from "always" (1 point) to "never" (5 points). Scores for each of the five questions are aggregated to give the final score which ranges from 5 to 25 points. Any score of less than 25 points is defined as non adherence to the medication [11]. If patient is non adherent to one OAD in the regimen, then patients was labeled as non adherent to the OAD(s) regimen. MARS-5 questionnaire was administered at enrollment as well as during each follow-up visit to evaluate adherence for each OAD [8].

If patient was found to be non adherent according to MARS-5 questionnaires, a list of reasons for non adherence was provided to the patients to select from. This list of reasons was prepared by taking in to reference of that used by Alshehri KA et al., [7]. Various reasons for the non adherence to the treatment were grouped as per the patient factors and doctor factors, healthcare management factors, or other specified reasons. The list was than validated by the faculty members.

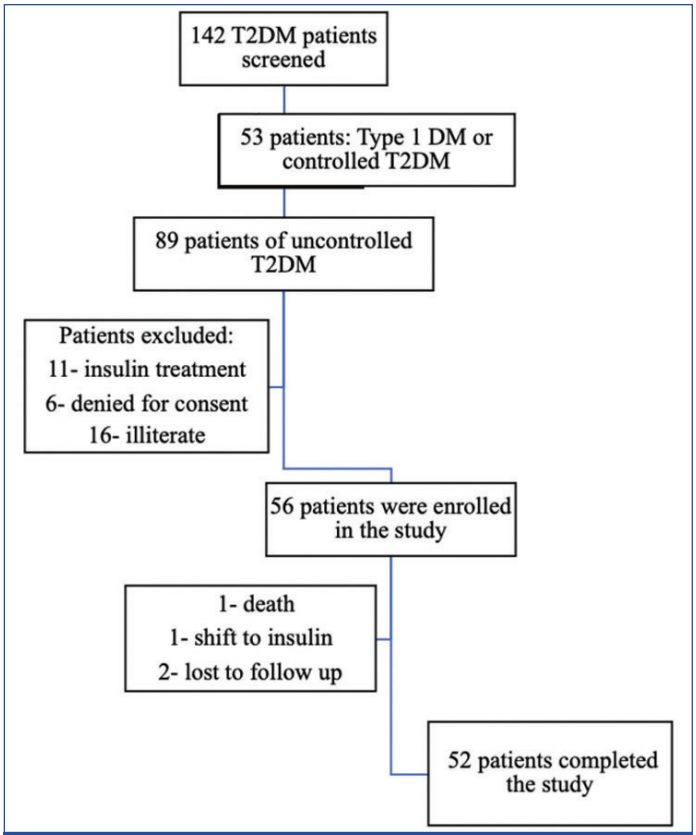
The ADRs were reported during the study period due to OAD(s) or concomitant drugs [12]. These were classified than as per system organ class, and the causal association was evaluated using World Health Organisation Uppsala Monitoring Centre (WHO-UMC) scale [13] and Naranjo score [14]. Severity of ADRs was assessed using Hartwig's scale [15], and preventability was determined using modified Schumock GT and Thornton JP scale [16].

STATISTICAL ANALYSIS

Demographic data and results for adherence to ADD and OAD(s) are expressed in percentage. Change in blood sugar levels was evaluated using Z test of significance, while association of adherence to improvement in blood sugar level was evaluated using Chi-square test of association at 95% confidence interval and $p<0.05$ was considered as statistically significant.

RESULTS

Out of 142 known cases of Type 2 Diabetes Mellitus (T2DM) screened, 89 patients had uncontrolled T2DM. Out of these 89 patients, 23 patients were excluded. Out of 56 enrolled patients, 52 completed the study [Table/Fig-1].



[Table/Fig-1]: Flow chart showing disposition of study participants.

Male to female ratio in the present study was 1.8:1 (20 males: 36 females). Mean age group and BMI were 57.14±10.3 years and 26.4±5.53 kg/m², respectively. Demographic details and other characteristics of the enrolled patients (n=56) are as shown in [Table/Fig-2]. Out of 56 patients, co-morbidities were present in 47 patients. Hypertension was the most common co-morbidity, seen in 45 patients, followed by hypothyroidism in 11 patients. Complaints were observed in 26 patients at time of enrollment, with most common being tingling sensation in lower and/or upper limbs (15 patients), followed by lower backache (5 patients).

Parameters	n (%)/Mean±SD
Gender	
Male	20 (36)
Female	36 (64)
Male: Female ratio	1.8:1

Age (years)	57.14±10.3
30-49	10 (18)
50-69	41 (73)
70-89	5 (9)
Body Mass Index (BMI) (Kg/m sq.)	26.4±5.53
<18.5 (Underweight)	4 (7)
18.5-24.9 (Normal)	18 (32)
25-29.9 (Overweight)	20 (36)
30 and above (Obese)	14 (25)
Addiction history	
Addiction present	5 (9)
No addiction	51 (91)
History of diabetes (years)	
Less than 1	2 (4)
1-5	24 (43)
6-10	13 (23)
11-15	12 (21)
16- 20	5 (9)
Co-morbidities	
Hypertension	45 (80)
Hypothyroidism	11 (18)
Chronic Obstructive Pulmonary Disease (COPD)	2 (6)
Ischaemic heart disease	2 (6)
Others*	4 (7)

[Table/Fig-2]: Demographic details and other baseline characteristics of patients of uncontrolled T2DM.
(n=56); *chronic stable angina and concentric left ventricular hypertrophy, cardiovascular stroke, epilepsy

There was a statistically significant decrease in the mean FBS and PPBS levels at 1st month follow-up (p-value <0.01) and at 6th month follow-up (p-value <0.001) compared to baseline [Table/Fig-3]. A statistically significant reduction (p-value <0.01) in mean HbA1c (%) at end of the study, compared to baseline. At the end of the study, HbA1c level were reduced to <7% in 33 patients (63%, n=52).

Laboratory investigations	(Mean±SD) at baseline (n=56)	(Mean±SD) at 1st month (n=56)	(Mean±SD) at 6th month (n=52)	Z test of significance	
				At 1st month compare to baseline	At 6th month compare to 1st month follow-up
Fasting Blood Sugar (FBS) (mg/dL)	212.94±60.98	174.15±42.41	136.47±20.11	p<0.01 (SE=12.38, Z=3.13)	p<0.001 (SE=13.69, Z=7.75)
Postprandial blood sugar (PP2BS) (mg/dL)	286.99±77.63	244.02±60.23	181.22±39.97	p<0.01 (SE=12.38, Z=3.13)	p<0.001 (SE=11.06, Z=5.69)
Glycosylated haemoglobin (HbA1c) (%)	8.55±0.83	-	6.85±0.83	-	p<0.01 (SE: 0.20; Z: 8.48)

[Table/Fig-3]: Mean change in FBS, PP2BS and HbA1c at baseline, 1st month and 6th month follow-up.
(Z test applied to compare mean reduction in FBS, PPBS and HbA1c. Data is expressed as mean±SD, SE and Z and p-value; n=52 at 6th month follow-up, as 52 patients completed all follow-up visit as per protocol)

Details of the OADs prescribed at enrollment and during follow-up were recorded. Percentage patients prescribed single OAD were decreased, and that described dual OADs regimen were increased during study period [Table/Fig-4].

Antidiabetic drugs regimen	No. of patients (%) (at enrollment n=56)	No. of patients (%) (during follow-up n=52)
Metformin and SUs*	15 (27)	13 (25)
Metformin, SUs and voglibose	7 (12.5)	7 (13)
Metformin	7 (12.5)	5 (10)
Metformin, SUs, voglibose and teneligliptin	15 (27)	14 (27)
Metformin, SUs and teneligliptin	12 (21)	11 (21)
Metformin and voglibose		1 (2)
SUs and teneligliptin		1 (2)

[Table/Fig-4]: Oral Anti-Diabetic Drugs (OAD) regimen prescribed in patients of uncontrolled T2DM.
*Sulfonylurea, **Metformin and voglibose; SUs and teneligliptin

At baseline, modification was made in OAD(s) regimen of all the enrolled patients, except three; and in 20 patients during subsequent follow-up [Table/Fig-5]. As far as individual OADs, are concerned, dose of metformin was increased in 27 and SUs in 9 patients. Tablet teneligliptin was added in 17 and voglibose in five patients. Mean±SD doses (mg) of metformin, glipizide, voglibose, teneligliptin, and glimepiride at baseline were 1982.14±377.54, 15.68±7.28, 0.78±0.28, 25.19±10.31, and 4.2±2.04, respectively.

During follow-up visit, OAD regimen was changed in 20 patients during follow-up visits. Dose of tablet teneligliptin was increased in eight and glipizide in five patients. A decrease in the dose and discontinuation of OADs during follow-up was seen in four patients due to ADR or shifting of the patient to insulin treatment.

During course of study, 41 patients achieved an adherence rate of 100%, while 14 patients had adherence rate of >80%. One patient was non adherent as per pill count method.

As per MARS-5 questionnaires, at time of enrollment, a total of 29 patients (52%, n=56) were adherent to the Anti-Diabetic Diet (ADD) and 44 (79%, n=56) to OADs. Follow-up trend for adherence to ADD and OADs is shown in [Table/Fig-6]. By the end of the study, 49 patients (94%, n=52) were adherent to ADD and 51 patients (98%, n=52) were adherent to OADs.

During follow-up, five patients who were initially adherent to OADs showed non adherence at different follow-up visit. Amongst the patients non adherent to OADs, seven patients were receiving four OADs (metformin, sulfonylureas [SUs], voglibose, and teneligliptin) and seven patients were receiving three OAD(s) regimen {metformin, SUs, and teneligliptin (6); and metformin, SUs, and voglibose}.

At enrollment, 12 patients were non adherent to OADs, and details of MARS-5 assessment for non adherence is as shown in [Table/Fig-7]. Reasons for non adherence included having many medications, traveling to distant place, complex regimen and interference due to routine work.

There was no significant association of FBS and PP2BS levels at 6th month follow-up visit with the adherence to ADD as well as OADs (p-value >0.5). Similarly, association between three-monthly

Changes in regimen	No of patients at enrollment (n=56)	No of patients at follow-up (n=52)
Increased in dose of already prescribed OAD(s)*	26 (46)	13 (25)
Addition of new OAD(s)	18 (32)	3 (6)
Increased in dose of already existing treatment and addition of new drug	9 (16)	-
No change in OAD(s) regimen	3 (6)	32 (61)
Discontinuation and/or decrease in the dose of drug in regimen with addition of new drug	-	2 (4)
Decrease in the dose of the drug	-	1 (2)
Discontinuation of drug	-	1 (2)

[Table/Fig-5]: Modifications in the Oral anti-diabetic drugs regimen at time of enrollment and during follow-up.
*Oral anti-diabetic drugs

HbA1c (%) in 50 patients with adherence to ADD and OADs (p-value >0.5) was statistically non significant.

Adherence	Baseline	Follow-up					
		1st	2nd	3rd	4th	5th	6th
ADD	29	46	49	43	44	45	49
OAD(s)	44	51	47	48	48	47	51

[Table/Fig-6]: Adherence of patients of uncontrolled T2DM to the Anti-Diabetic Diet (ADD) and oral anti- diabetic drugs OADs (n=56).
ADD: Anti diabetic-diet; OAD(s): Oral anti-diabetic drugs

Question no.	Reason	No. of patients	Reasons for non adherence*	No. of patients
At time of enrollment				
1	Forget dose of medicine	7	Many medication	4
			Travelling	3
			Complex regimen	3
			Interference with routine	2
2	Skipped dose of medicine	2	Fasting	1
			Many medication	1
			Feeling dose is high	1
3	Alter dose of medicine	-	-	-
4	Less medicine taken than prescribed	2	Many medications	2
			Complex regimen	1
5	Medication stopped	1	Hospital closed during follow-up so waited a week	1
During follow-up visits				
1	Forget dose of medicine	9	Travelling	6
			Complex regimen	2
			Many medication	2
			Tensed mood	1
			Interference with routine	1
2	Skipped dose of medicine	6	Fasting	3
			Complex regimen	2
			Interference with routine	2
			Death in family	1
3	Alter dose of medicine	-	-	-
4	Less medicine taken than prescribed	2	Many medications	1
			Fasting	1
5	Medication stopped	-	-	-

[Table/Fig-7]: MARS-5 assessment for non adherence to oral Anti-Diabetic Drugs (OADs) in patients of uncontrolled T2DM during study period.
*more than one reason was given by each patient as a reason for non adherence

A total of seven ADRs were reported by six patients during the study period, as detailed in [Table/Fig-8]. All patients recovered from the ADRs with appropriate treatment.

DISCUSSION

Out of 142 known cases of T2DM screened, 89 patients had uncontrolled T2DM, of which 56 patients were included in the study and followed-up every month for six months. Fifty-two patients completed the study. A statistically significant reduction (p-value <0.001) was observed in FBS and PP2BS at the end of study, while HbA1c% reduced to <7% in 33 patients (63%, n=52). Percentage improvement in adherence to the ADD and OAD(s) among the enrolled patients during the study period. At the end of the study, 3 patients (6%) were non adherent to the ADD, and one patient was non adherent to the OAD(s).

In the present study, mean age of enrolled patients was 57.14±10.3 years. Studies have reported a higher incidence of T2DM in 50-59 years [17]. Deterioration of beta cell function with progressing age and pill burden due to multiple co-morbidities might be the risk factor for uncontrolled T2DM in this age group [18-20].

In the present study, out of 56 patient majority (36, 64%) were female patients, which was similar to a study by Aravindakshan MR et al., reported 65% of uncontrolled T2DM patients were female [21]. Females in the menopausal age group shows substantial decrease in endogenous oestrogen, altered adipose tissue distribution, decreased energy expenditure and insulin sensitivity, increased weight and insulin secretion, predisposing them to the development of uncontrolled T2DM [22,23].

In the present study, 34 patients (61%) were classified as overweight or obese (BMI>kg/m^2), with an average BMI of 26.4±5.53 kg/m^2 (Mean±SD). Obesity is one of the strongest risk factors for poor glycaemic control, as it causes insulin resistance [20,24]. Duration of T2DM was more than one year in 54 patients (98%), with 24 patients (43%) having a history of diabetes between 1 and 5 years. An increasing duration of diabetes is associated with deterioration in pancreatic β cells, leading to poor glycaemic control, which could have led to uncontrolled diabetes [21]. Hypertension was the most common co-morbidity seen in 45 (80%) patients, in the present study, which was similar to a study by Begum N et al., [25]. The incidence of hypertension in patients with T2DM is approximately two-fold higher than in age-matched subjects without the disease [26], due to increased peripheral artery resistance caused by vascular remodeling and increased body fluid volume due to insulin resistance-induced hyperinsulinemia and hyperglycaemia [27]. Hypertension has also been identified as a major risk factor for development of diabetes and its micro- and macrovascular complications [28].

In the present study, there was statistically significant reduction in FBS and PP2BS, from 212.94±60.98 mg/dL to 136.47±20.11 mg/dL and from 286.99±77.63 mg/dL to 181.22±39.97 mg/dL, respectively, at end of the study compared to the baseline. Mean HbA1c (%) reduced from 8.55±0.83% at baseline to 6.85±0.83%. Improvements in the glycaemic index could be due to sensitisation of the patients for monthly follow-up, with regular assessment leading to timely

S. No.	ADR	Suspected drugs	WHO- UMC category	Naranjo score	Hartwigs scale	Modified Schumock GT and Thornton JP scale	SOC classification
1	Constipation	Teneligliptin, Metformin, Glimepiride	Possible	2	Mild	Non preventable	Gastrointestinal disorders
2	Gastric upset	Pregabalin+methylcobalamin, Metformin, Glipizide, Teneligliptin	Possible	2	Mild	Non preventable	Gastrointestinal disorders
3*	Easy fatigue/hypoglycaemia	Glipizide	Certain	7	Mild	Non preventable	Endocrine disorders
4*	Gastric upset	Metformin, Glipizide, B complex, Folic acid	Possible	2	Mild	Non preventable	Gastrointestinal disorders
5	Easy fatigue/hypoglycaemia	Glipizide, Metformin	Probable	4	Mild	Non preventable	Endocrine disorders
6	Dizziness	Metformin, Glipizide, Losartan, Amlodipine Metoprolol	Possible	2	Mild	Non preventable	Central nervous system disorders
7	Dry cough	Enalapril	Certain	5	Mild	Non preventable	Respiratory tract disorders

[Table/Fig-8]: Adverse Drug Reaction (ADR) observed in the T2DM patients during the study period.
*ADR of Sr. no. 3 and 4 were observed in same patient

treatment modifications. Additionally, emphasis on adherence to ADD and OADs by physician at each follow-up visit might have contributed to improved glycaemic control.

Metformin is the treatment of choice among The OADs for all patients, as was observed in the present study. Metformin reduces both macrovascular as well as microvascular complications of diabetes, retards β-cell failure, aids in weight reduction and reduces the risk of myocardial infarction and stroke. Preferred second-choice of the drug as per guidelines, include sulfonylureas (SUs), dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), such as teneligliptin, and sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors), including canagliflozin, dapagliflozin, and empagliflozin. However, in the present study, second-line drugs were usually selected from SUs, DPP-4 inhibitors, and alpha-glucosidase inhibitors (voglibose) as per availability at the study site [1,29,30].

At the time of enrollment, 19 (34%, n=56) patients were prescribed triple-drug regimen (metformin, SUs, and teneligliptin; metformin, SUs, and voglibose), followed by quadruple drug regimen, which included 15 patients (27%) (metformin, SUs, voglibose, and teneligliptin), and dual-drug regimen for another 15 patients (27%) (metformin and SUs), followed by metformin monotherapy (7, 13% patients). This trend remained same throughout the study period. Dose range of individual OADs seen in present study were on the higher side, possibly owing to uncontrolled nature of the disease.

At baseline, 29 patients (52%) were adherent to the ADD, while at the end of the study, 49 patients (94%) were adherent to the ADD. As per MARS-5 assessment, at baseline, 44 patients (79%) were adherent to the OADs, and at the end of study, this number increased to 51 (98%). Sensitisation of the patients due to implementation of various methods for drug adherence, i.e., drug adherence diary, pill count and MARS-5 questionnaires, as well as reinforcement of importance of adherence at each follow-up visit by the physician, contributed to the improvement observed in the adherence to ADD and OADs in the present study.

It is important to note that pill counts cannot verify whether a dose removed from a drug strip was actually consumed in actual or not [10]. So, additionally MARS-5 questionnaire method for adherence was implemented and evaluated. However, results of adherence to medications using MARS-5 adherence questionnaires could be affected due recall bias [11]. Drug adherence diary to be filled up daily for six months might have acted as a trigger at home for the patient to become self-aware for compliance to diet and medications. This could have reduced the chances of manipulation for pill count and subjective variations in MARS-5 assessment.

In present study, 16 patients forgot to take medicines at baseline or follow-up, as per MARS-5 assessment, followed by 8 patients who skipped the dose of medicines; four patients took less medicine than prescribed dose and one patient stopped the medication as per MARS-5 scale. In the present study, majority of the patients gave reasons for non adherence to antidiabetic medication: as many medications, 9 patients mentioned traveling to distant places (9 patients indicated a complex regimen, and 5 patients cited interference with routine work.

Patients showing non adherence to OADs were mainly prescribed triple or quadruple drug regimens. Recent data suggest that the overall complexity of the T2DM medication regimen predicts adherence, with greater complexity contributing to poorer adherence [31].

With improvement in the adherence to ADD and OADs, there was also an improvement in glycaemic control. However, an association between improvement in adherence to ADD and OADs and improved glycaemic parameters like FBS, PPBS and HbA1c was statistically insignificant. This finding was similar to the study carried out by Balkhi B et al., [32]. In the present study, major SOC class of ADRs were gastrointestinal disorders, followed by metabolic disorders, which was similar to the study by Begum N et al., [25].

Regular assessment of enrolled patients of T2DM allowed for strict monitoring of blood glucose level and sensitising patients regarding adherence to ADD and OADs by the physician. It helps to timely modify OADs and also treat ADRs that may have occurred. The use of drug adherence diary, pill count method, as well as a self-administered report scale (MARS-5 questionnaires) aided in avoiding subjective variation in assessment of adherence.

Limitation(s)

Assessment of outcomes was carried out for only six-months duration, but a longer duration of follow-up might help in evaluating long-term glycaemic control. Additionally, this was a single-centred study conducted at a tertiary care teaching hospital, where treatment is provided free of cost, so study sample included patients mainly from poorer socio-economic class. Further as drug adherence diary was implemented as assessment tool, so illiterate patients could not be included in the study.

CONCLUSION(S)

Monthly follow-up of the study patients helped in timely diagnosis of poor glycaemic control and appropriate treatment modification and counseling for strict adherence to lifestyle modifications and pharmacotherapy. Percentage patients prescribed single OAD decreased, and that described dual or triple OADs regimens increased during the study period. By the end of the study, >90% of the patients had become adherent to ADD and OADs. More concomitant drugs due to uncontrolled disease as well as co-morbidities leading to complex drug regimen, tend to lower the drug adherence which in turn, affect glycaemic control. Methods like implementation of drug adherence diary act as a trigger at home, for the patients to become self-aware for compliance to diet and medications. Regular implementation of different tools for drug adherence evaluation in uncontrolled T2DM patients reinforces the importance of treatment adherence to the patients for better therapeutic outcomes.

REFERENCES

[1] International Council of Medical Research. Diabetes guideline. [Internet]. [cited 2023 Jan 23]. Available from: https://medibulletin.com/wp-content/uploads/2021/05/ICMR.diabetesGuidelines.2021.pdf.

[2] Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88-98.

[3] Coronary artery disease in India. CADI research foundation. Diabetes in South India. [Internet]. [cited 2023 Jan 23]. Available from: https://cadiresearch.org/topic/diabetes-indians/diabetes-south-india.

[4] American Diabetes Association, Standards of medical care in diabetes—2021 abridged for primary care providers. Clin Diabetes. 2021;37(1):11. [cited 2023 Jan 23]. Available from: https://pubmed.ncbi.nlm.nih.gov/33551551/.

[5] Anusuya GS, Ravi R, Gopalakrishnan S, Abiselvi A, Stephen T. Prevalence of undiagnosed and uncontrolled diabetes mellitus among adults in South Chennai. Int J Commun Med Pub Health. 2018;5(12):5200-04.

[6] Anghel LA, Farcas AM, Oprean RN. An overview of the common methods used to measure treatment adherence. Med Pharm Rep. 2019;92(2):117-22.

[7] Alshehri KA, Altuwaylie TM, Alqhtani A, Albawab AA, Almalki AH, Albawab A. Type 2 diabetic patients adherence towards their medications. Cureus. 2020;12(2):e6932.

[8] Lee CS, Tan JH, Sankari U, Koh YL, Tan NC. Assessing oral medication adherence among patients with type 2 diabetes mellitus treated with polytherapy in a developed Asian community: A cross-sectional study. BMJ Open. 2017;7(9):e016317.

[9] Weir CB, Jan A. BMI classification percentile and cut off points. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. [Updated 2023 Jun 26]. Available from: https://www.ncbi.nlm.nih.gov.

[10] Ogawa N, Takahara M, Shiraiwa T, Yamamoto M, Yamamoto K, Doi M, et al. Improved treatment satisfaction and medication adherence after readjusting oral medication regimens with the cooperation of health insurance pharmacy in type 2 diabetic patients in Japan. J Pharm Health Care Sci. 2017;3:27.

[11] Chan AH, Horne R, Hankins M, Chisari C. The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of non-adherence. Br J Clin Pharmacol. 2020;86(7):1281-88.

[12] Hashim R, Zainal ZA, Taib HM. Preliminary report: Review of adverse drug reactions (ADRs) reporting in the Malaysian elderly. Pharm Sci Asia. 2019;46(3):135-39.

[13] World Health Organization, Uppsala Monitoring Centre. The Use of WHO-UMC System for Standardised Case Causality Assessment. World Health Organization (WHO)- Uppsala Monitoring Centre. [cited 2023 Jan 18]. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_asses sment.pdf.

[14] Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.
[15] Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992;49(9):2229-32.
[16] Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992;27(6):538.
[17] Al-Saeed AH, Constantino MI, Molyneaux L, D'Souza M, Limacher-Gisler F, Luo C, et al. An inverse relationship between age of type 2 diabetes onset and complication risk and mortality: The impact of youth-onset type 2 diabetes. Diabetes Care. 2016;39(5):823-29.
[18] Bellary S, Kyrou I, Brown JE, Bailey CJ. Type 2 diabetes mellitus in older adults: Clinical considerations and management. Ant Rev Endocrinol. 2021;17(9):534-48.
[19] Pratley RE, Gilbert M. Clinical management of elderly patients with type 2 diabetes mellitus. Postgraduate Med. 2012;124(1):133-43.
[20] Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci. 2020;21(13):4725.
[21] Aravindakshan MR, Maity SK, Paul A, Chakrabarti P, Mandal C, Sarkar J. Distinct pathoclinical clusters among patients with uncontrolled type 2 diabetes: Results from a prospective study in rural India. BMJ Open Diabetes Research and Care. 2022;10(1):e002654.
[22] Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endo Rev. 2016;37(3):278-316.
[23] Paschou SA, Anagnostis P, Pavlou DI, Vryonidou A, Goulis DG, Lambrinoudaki I. Diabetes in menopause: Risks and management. Curr Vasc Pharmacol. 2019;17(6):556-63.
[24] Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma YZ, et al. Assessment of skeletal muscle triglyceride content by 1H nuclear magnetic resonance spectroscopy in lean and obese adolescents: Relationships to insulin sensitivity, total body fat, and central adiposity. Diabetes. 2002;51(4):1022-27.
[25] Begum N, Prahlad B, Bhawani G. Drug utilization study of antidiabetic drugs in a tertiary care hospital. The Pharma Innovation J. 2019;8(6):1033-38.
[26] Miller GJ, Maude GH, Beckles GL. Incidence of hypertension and non-insulin dependent diabetes mellitus and associated risk factors in a rapidly developing Caribbean community: The St James survey, Trinidad. J Epidemiol Community Health. 1996;50(5):497-504.
[27] Ohishi M. Hypertension with diabetes mellitus: Physiology and pathology. Hyperten Res. 2018;41(6):389-93.
[28] Kim MJ, Lim NK, Choi SJ, Park HY. Hypertension is an independent risk factor for type 2 diabetes: The Korean genome and epidemiology study. Hyperten Res. 2015;38(11):783-89.
[29] Powers AC, D'Alessio D. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. Goodman and Gilman's, The Pharmacological Basis of Therapeutics. 13th Ed. New York: McGraw-Hill. 2011; pp.1237-271.
[30] Tripathi KD. Insulin, oral hypoglycaemic drugs and glucagon. Essentials of Medical Pharmacology 8th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Lt. 2019; pp. 280-305.
[31] Al Bawab AQ, Al-Qerem W, Abusara O, Alkhatib N, Mansour M, Horne R. What are the factors associated with nonadherence to medications in patients with chronic diseases. Healthcare (Basel, Switzerland). 2021;9(9):1237.
[32] Balkhi B, Alwhaibi M, Alqahtani N, Alhawassi T, Alshammari TM, Mahmoud M, et al. Oral antidiabetic medication adherence and glycaemic control among patients with type 2 diabetes mellitus: A cross-sectional retrospective study in a tertiary hospital in Saudi Arabia. BMJ Open. 2019;9(7):e029280.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Pharmacology, B. J. Medical College, Ahmedabad, Gujarat, India.
2. Assistant Professor, Department of Pharmacology, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India.
3. Professor, Department of Pharmacology, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India.
4. Associate Professor, Department of Pharmacology, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India.
5. Professor and Head, Department of Pharmacology, B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Samiksha J Sonar,
205, Shivam Apartment, Opposite Jay Gayatri Nagar Society, V.I.P. Road, Karelibaugh, Vadodara-390022, Gujarat, India.
E-mail: samy1211997@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 23, 2024
- Manual Googling: Oct 15, 2024
- iThenticate Software: Nov 05, 2024 (12%)

ETYMOLOGY: Author Origin

EMENDATIONS: 10

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 22, 2024**
Date of Peer Review: **Aug 22, 2024**
Date of Acceptance: **Nov 07, 2024**
Date of Publishing: **Apr 01, 2025**

[ANNEXURE I]

MARS-5 (QUESTIONNAIRES)

1. Do you forget taking your diabetes medicines? Yes No
   [1] Always [2] Often [3] Sometimes [4] Rarely [5] Never
2. Do you skip/miss out the dose/s of your diabetes medicines? Yes No
   [1] Always [2] Often [3] Sometimes [4] Rarely [5] Never
3. Do you alter the dose of your diabetes medicines? Yes No
   [1] Always [2] Often [3] Sometimes [4] Rarely [5] Never
4. Do you take less medicines then prescribed? Yes No
   [1] Always [2] Often [3] Sometimes [4] Rarely [5] Never
5. Have you ever stopped taking your diabetes medicines? Yes No
   [1] Always [2] Often [3] Sometimes [4] Rarely [5] Never

Final total score:……/25.

Inference:……...

Select the most appropriate reasons from below, if inference is showing low adherence.

Reasons	Yes	No
Drug factors		
• Many medications		
• Complex regimen		
• Interference with the routine		
• Adverse effect of the drug		
Patient factors		
• Feeling that the given dose is high		
• Feeling that the treatment is ineffective		
• Lack of family support		
• Lack of finance		
• Lack of knowledge of patients for disease management		
• Concomitant illness		
• Fasting		
• Travelling to distant places		
• Following advice from peers or relatives		
• Following other measures for diabetes management		
• Frequent follow-up of patients staying distantly		
• Non availability of doctor with whom patient wants to get consulted		
Health system or doctors factor		
• Non availability of drugs		
• Lack of time to doctor, due to patient overload		
• Communication gap with patient or difficulty in understanding language of each other		
• Inadequate sensitisation from doctor regarding disease and its management		

Other (s): -……
……
……

[ANNEXURE II]

Drug Adherence Diary: Follow-up month

Weeks	Drugs	Mon	Tue	Wed	Thurs	Fri	Sat	Sun
1st week								
2nd week								
3rd week								
4th week								
5th week								