Research Article

Prescription pattern and cost variation analysis in type 2 diabetes mellitus patients at private outpatient department

Short title: Prescription Pattern and Cost Analysis of Oral Antidiabetic Drugs

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ABSTRACT

Introduction: Diabetes is regarded as 21st century's epidemic. To prevent complications, apart from life style modification pharmacotherapy is required to control blood sugar. Even though many oral antidiabetic drugs are available, satisfactory/target glycaemic control is not achieved. Cost of drug therapy is an important factor influencing compliance with treatment, particularly chronic diseases. So, need for periodic evaluation of prescription of diabetic patients.

Aims and objective: To analyse pattern of antidiabetic drug prescriptions and percentage cost variation of prescribed antidiabetic drugs.

Methods: This was a cross sectional observational study conducted among type 2 diabetes patients aged>12 yrs (either gender) at Out Patient Department (OPD) of private diabetes clinic during 2018-2019. Juvenile diabetes, gestational diabetes, indoor patients were excluded from the study. Patients were interviewed and details were filled up in case record form. Socio-demographic data, prescription pattern, percentage cost variation and cost ratio were analyzed.

Result: Total 349 patients were enrolled with mean age 53 ± 12 years. Average no. of antidiabetic drugs per prescription was 3.34. Majority (96.56%) patients were prescribed at least one Fixed Dose Combination (FDC). Most common FDC was (97.99%) with biguanides and sulfonylureas. FDC with Metformin (500 mg) and glimepiride (2 mg) had maximum percentage cost variation (712.20) and very high cost ratio (8.12). Satisfactory glycemic levels were achieved in 58.45% patients.

Conclusion: Polypharmacy, overuse of FDC'S with vast percentage cost variation and high cost ratio was observed. Need to pay attention towards diabetic education training, rational treatment approach and pricing control of medicine by regulatory agency.

Key words: T2DM; FDC; Metformin; Hypoglycemia; SUR

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INTRODUCTION

Diabetes is regarded as 21st century's epidemic [1]. According to National Diabetes and Diabetic Retinopathy Survey report the prevalence of diabetes in India was 11.8% in the last four years (2015-2019) and Gujarat contributed highest (20.5% of the total) [2]. Type 2 Diabetes Mellitus (T2DM) accounts for 90%–95% total cases of diabetes in adult. Glycemic control is necessary to slow the progression of such microvascular and macrovascular complications [3,4]. Majority diabetics require oral antidiabetic drugs to achieve glycemic control apart from life style modification. Even though various oral antidiabetic drugs are available with many brands, satisfactory/target glycaemic control is not achieved. Cost of drugs is an important factor influencing compliance with treatment particularly chronic disease [5]. So Periodic evaluation of variability in prescription pattern is essential for understating drug use and cost variation. The present study was conducted to analyse the current prescribing pattern of oral antidiabetic drugs in T2DM with cost variation in outpatient department at private diabetes clinic in Rajkot.

MATERIALS AND METHODS

This was a cross sectional observational study conducted at Out Patient Department (OPD) of private diabetes clinics during year 2018-2019, after approval from institutional ethic committee. Study included type 2 diabetes patients aged more than 12 years, either gender and had taken treatment with oral hypoglycemic agents for minimum 3 months of duration. Juvenile diabetes, gestational diabetes, indoor patients were excluded from the study. After obtaining informed consent, patients were interviewed and details regarding sociodemographic, antidiabetic drug therapy, adverse effects, co morbidity and investigations were filled up in case record form. Data were collected on two working days per week during study duration. Assessment of satisfactory glycaemic control was evaluated by achievement of target value set by Indian Medical Council Research (ICMR) guideline for diabetes (of Fasting Blood Sugar (FBS)/ post prandial blood sugar/glycosylated haemoglobin Hb1c/random blood sugar (RBS)} [6]. Sample size calculation: The estimated sample size was determined by using the single proportion formula, where n=the desirable sample size; Z (α/2)=the confidence interval (95%) level of significance (1.96); p=prevalence of DM in Gujarat and d=precision of measurement (acceptable marginal error). The values were p=0.2 and d=0.08.

The cost of antidiabetic drugs in Indian rupee (₹-INR) for 10 tablets was calculated for each prescribed brand of Oral Hypoglycemia Drugs (OHA). The percentage cost variation and cost ratio were then calculated for each individual for drug strength in formulation. The percentage variation in the cost of the drugs was calculated using the following formula [5]. Percentage cost ratio: [(Price of most expensive brand-Price of least expensive brand)/(Price of least expensive brand)] × 100

Price of least expensive brand Cost ratio was calculated by the ratio of most expensive brand to least expensive brand of the same drug, 12

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Drugs with no cost information and prescribed with only one brand name were excluded. Data were entered in Microsoft office excel 2016 and descriptive statistical analysis was done.

RESULTS

Out of 385 enrolled T2DM patients, analysis was done among 349 patients (after exclusion of those who had not data of glycemic control) More than half (58%) of total participants were in middle age group (41-60 yrs). Majority participants had high BMI (71.45%), were literate (73.06%) and married (99.42%). Average disease duration of study participant was 8.1 ± 6.6 years. Co morbidity was associated with 42.97% T2DM participants (mean age was 52.91 ± 12.77 years). Diabetes complications were observed in 7.16% of study patients. Smoking was reported in 14.67% only in male participants (Table 1).

Table 1: Sociodemographic details of participant

Sociodemographic parameters	Number of patients, N=349 (%)
Age (year) (mean+SD)	53 ± 12
Male/ Female	52.72/ 47.27
BMI (body mass index-kg/ m2)	7104.17 (± 1.72)
Normal weight (18.5-24.9),	101 (28.94),
Over weight (25-29.9),	145(41.54),
Obesity (>30)	103(29.51)
Duration of diabetes (year)	7104.17 (± 1.72)
≥ 10,	264(75.64).
11-20,	63(18.05),
21-30	19(5.44)
Co Morbidly	7104.17 (± 1.72)
Hypertension,	100 (28.65),
Dyslipidaemia,	45(12.89),
Thyroid disorder,	5(1.43),
Benign prostatic hyperplasia	3(0.85)
Diabetic complication	7104.17 (± 1.72)
Nephropathy,	12 (3.49),
Peripheral neuropathy,	5(1.43),
Peripheral vascular disease,	5(1.43),
Retinopathy, diabetic foot.	3(0.85),
No. of antidiabetic drugs per prescription	7104.17 (± 1.72)
≤ 3 antidiabetic drugs	205(58.73)
4 antidiabetic drugs	144 (41.26)

Average no. of antidiabetic drugs per prescription was 3.34 in our study. Only 3.43% of patients were prescribed monotherapy rest (96.56%) were prescribed at least one fixed dose combination (FDC). Few patients (5.73%) were prescribed insulin in addition to oral hypoglycemic agents. Majority patients were prescribed 2 drugs (32.09) followed by 3 drugs (23.20) and 5 drugs (21.20) per prescription. FDC (with two antidiabetic drugs-88.25%) were more commonly prescribed than FDC (with three antidiabetic drugs-19.19%). Two FDCs per prescription was observed in 10.88% of T2DM patients (Table 2).

Table 2: Number of the antidiabetic drugs per prescription

No. of antidiabetic drugs per prescription	Frequency (%) (N=349)
1	12 (3.43)
2	112(32.09)
3	81(23.20)
4	55(15.75)
5	74(21.20)
6	15(4.29)

Biguanides (Metformin) was most common (97.99%) component of FDC in this study. Among other oral hypoglycemic agents in FDCs, sulfonylurea was most frequently (62.75%) combined followed by DPP-4 inhibitors (21.20%) (Table 3).

Table 3: Prescribing pattern of antidiabetic drugs

FDC (No. of antidiabetic groups) (frequency)	Individual drug (frequency)
FDC (2)* (Two antidiabetic groups) (n=302)	144 (41.26)
Biguanides+Sulfonylurea (219)	Metformin+Gliclazide (94)
	Metformin+Glimepiride (89)
	Metformin+Glibenclamide (22)
	Metformin+Glipizide (14)
Biguanides+DPP4-inhibitors (74)	Metformin+Teneligliptin (47)
	Metformin+Vildagliptin (16)
	Metformin+Sitagliptin (10)
	Metformin+Linagliptin (1)
Biguanides+PPAR activator (4)	Metformin+Pioglitazone (4)
Biguanides+SGLT2 inhibitors (2)	Metformin+Dapagliflozin (2)
Biguanides+α glucosides inhibitor (03)	Metformin+Voglibose (2)
	Metformin+Acarbose (1)
FDC (3) ** (Three antidiabetic drugs) (n=67)	144 (41.26)
Biguanides+Sulfonylurea+PPAR activator(56)	Metformin+Glimepiride+Pioglitazone (32)
	Metformin Glimepiride+Pioglitazone (16)
	Metformin+Gliclazide+Pioglitazone (8)
Biguanides+Sulfonylurea+α glucosides inhibitors (11)	Metformin+Glimepiride+Voglibose (11)

Table 4: Percentage cost variation and cost ratio of prescribed anti-diabetic drugs

Drugs	Strength (mg)	MOST expensive price (INR)	Least expensive price (INR)	Cost ratio	Percentage of cost variation
Metformin+ Glimepiride	500+0.5	88	24.36	3.6	261.72
	500+1	129	53	2.43	143.39
	500+2	157	19.33	8.12	712.2
	400+3	95	53	1.79	79.24
	1000+3	72.8	65	1.12	12
	500+4	108	53	2.03	103.77
	500+5	119	38.93	3.05	205.51
Metformin+Gliclazide	500+40	65	37	1.75	76.67
	500+80	135	53	2.54	154.71
Metformin+Glibenclamide	500+5	129	33	3.9	290.9
Metformin+Glipizide	500+5/10	13.94	7.2	1.93	93.61
Metformin+Teneligliptin	500+20	117	61	1.91	91.8
Metformin+Sitagliptin	500+50	348	125	2.784	178.4
Metformin+Glibenclamide+Pioglitazone	500+5+15	166	59	2.81	181.35
Metformin+Glimepiride+Pioglitazone	500+2+15	119	59	2.01	101.69
Metformin+Glimepiride+Voglibose	500+2+0.2	183	145	1.26	26.2
Metformin+Glimepiride+Voglibose	1000+2+0.2	279	103	2.7	170.87

Total N was not mentioned in table as more than one FDC were in many prescriptions,

*FDC (2): two antidiabetic drugs in FDC, **FDC (3): three antidiabetic drugs in FDC

FDC with Metformin (500 mg) and glimepiride (2 mg) had maximum percentage cost variation (712.20) and very high cost ratio (8.12) followed by FDC containing metformin (500 mg) and glibenclamide (5 mg). Lowest percentage cost variation and cost ratio (1.12) was observed with FDC containing metformin (1000 mg) and glimepiride (0.5 mg). 58.45% participants achieved glycemic control (Table 4).

DISCUSSION

High frequency of DM was observed in our study is, in middle age (41-50 years). DM is a disease of adult population as observed by many studies within India, [7-9] and in other developing and developed countries [1,10-12]. Greater prevalence in this age group may be due to change in life style, lack of exercise and stress [13]. The prevalence of DM increased with age, low physical activity, central obesity and high BMI [1-10]. The duration of diabetes plays a key role for its management [8]. Half of study participants had onset duration of diabetes less than 5 years. Average disease duration in diabetic patients with complication was 12 years.

Regarding comorbidities, in agreement with several studies, hypertension, dyslipidaemia, obesity, as well as cardiovascular and peripheral vascular diseases were observed as most common diabetes-associated comorbidities. In this study hypertension was commonest comorbidity (28.65%). Prevalence of hypertension in T2DM patients were observed in the range of 33% to 54% in various studies [7]. This high prevalence of hypertension with diabetes was associated with increased stiffness of large arteries, which often precedes macro vascular events [8]. Overweight or obesity was high (71%) among study participants in this study. Among all the factors studied, obesity emerged as the single-most modifiable risk factor for T2DM [14]. According to several cohort study as well as cross-sectional study from all around the world, overweight or obesity and central obesity as important risk factors for T2DM [7,14]. Moderate and sustained weight-loss (five percent to ten percent of body weight) can improve insulin action, decrease fasting glucose concentrations and reduce the need for diabetes medications [15].

Average number of oral antidiabetic drugs per prescription was 3.34 in this study which was higher in compare to other studies [4,16]. The WHO proposes, that optimally, this should be <2.15 [17]. In middle age, association of co-morbidity with T2DM is high so there are chances of polypharmacy. Prescribing minimum number of drugs per prescription is intended to avoid polypharmacy and thereby minimizing risk of drug-drug interaction, side effects, complication and cost too. Since average duration of diabetes in this study is 5.5 years the tendency for polypharmacy was observed to obtain glycaemic targets. With discovery of new drugs, pharmacotherapy of DM management has changed in last few decades. Almost all participants were prescribed FDCs in this study, which was higher in comparison to other studies done in India [4,17]. This shows new trends of prescribing dual or combination therapy in DM. A country like India where health care is not universally provided by the government, the cost burden of diabetes care falls directly on the patient, and FDCs help to reduce the economic burden on patients with diabetes [18]. Although FDCs are associated with many advantages like synergistic action, reduced adverse effects, reduced pill burden, cost of the treatment and improved patient's compliance but certain disadvantages like incompatible pharmacokinetics, inflexible dose ratio and increased toxicity are limiting factors [19]. According to Kamni S, study done on FDC for treatment of diabetes in Indian market concluded that 62% of the FDCs were irrational [19].

Metformin (with dose range 400-1000 mg/day) was most common component in all FDCs similarly in other studies also [16, 20,21]. Metformin is first drug to be used in accordance with National Institute Health and Care and Excellence (NICE) American Diabetes Association(ADA) and Indian Council of Medical Research (ICMR) [6] guidelines for the management of T2DM [22,23]. Metformin as first-line therapy has beneficial effects on HbA1C, weight, and cardiovascular mortality [24]. it is the drug of choice for overweight and obese (body mass index above 23 kg m-2) T2DM [9,24]. Metformin has the strongest evidence and has demonstrated long-term safety as pharmacologic therapy for diabetes prevention [25]. A recent metanalysis demonstrated superior results of the metformin combination therapy with better HbA1c reduction than alone metformin [26].

FDCs of biguanides and sulfonylurea (Gliclazide, glimepiride, glibenclamide) were most commonly prescribed in this study and remain as first choice in similar studies too [4,9,16]. Other OHA groups combined with biguanides were DPP-4 inhibitors (teneligliptin) and PPAR-γ activators (pioglitazone) in this study [9]. The review suggests that the most widely used component of FDCs is metformin with other OHAs such as glimepiride, pioglitazone, rosiglitazone, acarbose, and sitagliptin [27]. Newer oral hypoglycemic agents were preferred in few cases only.

In FDC biguanides and SUR (Glimepiride, Glibenclamide) was common and additional group added were PPAR-activator (pioglitazone) and alfa glucosides inhibitors (voglibose) [3]. Similar prescribing behaviour observed in other study also [9].

Diabetes Prevention Program Outcomes Study (DPPOS) suggested periodic testing of vitamin B12 as metformin use is associated with vitamin B12 deficiency and worsening of symptoms of neuropathy [22,23]. Measurement of serum vitamin B12 was done in 60 (17.19%) participant and out of them 11 (3. 15%) participants had low serum vitamin B12 (<200 ng/ml). Periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anaemia or peripheral neuropathy [28].

Cost ratio and percentage cost variation is variable among different strengths of same drugs in FDC. Cost ratio helps to know how many times the most expensive formulation is costlier compared to least expensive formulation. Highest percentage cost variation (metformin 500 mg+glimepiride 2 mg) and lowest percentage cost variation (metformin 1000 mg+glimepiride 0.5 mg) was with same drugs but with different strengths in this study. This combination is approved by CDSCO. Such price variation could be due to existing market structure of the pharmaceutical industry, asymmetry of information, industry costs and government regulations and pricing policies [5]. Due to the long-term treatment duration, diabetes patients usually have higher than average monthly out-of-pocket expenses and high out-of-pocket expenses which can be a barrier to adherence to prescribed drug regimens [5]. So cost factor in antidiabetic therapy is important for compliance in diabetes patient and treatment outcome too.

Government and Medial Council of India (MCI) promotes use of generic drugs, but in this study, all FDCS were prescribed by brand name suggesting popularity of the brands among the physician and influence of pharmaceutical companies on the physician. 82.52% FDCs prescribed in this study were approved by Central Drug Standard Control Organisation (CDSCO) [29]. National Essential Medicine List (NELM 2015) has not included any FDC of antidiabetic drugs [30].

Satisfactory glycemic control was achieved among 58.45% of study patients. Several studies have documented glycemic control ranges from 50% to 86% [4]. Age, educational level, duration of diabetes treatments, life style and physical exercise, co morbidity, self-awareness about disease progress and target control will affect glycemic control. In this study glycemic control was not significantly associated with age, gender, duration of illness, socioeconomical status and co morbidity. Satisfactory glycemic control was observed among 64.9% patients who were prescribed three or less than three antidiabetic drugs as compared to 49.7% of the patients among those who were on four or more antidiabetic drugs, this difference is statistically significant (2= 8.08, P,0.01). Self-management is a key element for the proper management, but strategies are currently lacking in the developing countries context [12].

CONCLUSION

Polypharmacy, overuse of FDC's, reliability on brands with high percentage cost variability was observed. This requires concerted effort from public, pharmacist, doctors and regulatory agencies to provide drugs/formulations to improve outcomes in chronic disease like T2DM.

Study limitation: The study was done for a short period of time and in smaller number of patients at one center.

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