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ORIGINAL RESEARCH

Adherence, satisfaction, and experience with metformin 500 mg prolonged release formulation in Indian patients with type 2 diabetes mellitus: a postmarketing observational study

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Purpose: The aim of this study was to understand patient adherence, satisfaction, and experience with the smaller sized metformin 500 mg prolonged release (PR) tablet that has been manufactured with the help of technological advancement (Gluformin I 500 mg), in comparison with metformin 500 mg extended-release (ER) tablet, in patients with type 2 diabetes mellitus (T2DM).

Patients and methods: In this postmarketing observational study, T2DM patients who were on a stable dose of metformin 500 mg PR tablet for at least 1 month and had previously received metformin 500 mg ER tablet were recruited from 50 sites in India. The medication adherence and patients' experience, satisfaction, and perception with metformin 500 mg PR tablets were compared with metformin 500 mg ER tablets. The patients' experience was determined based on the external appearance of tablet, ease of swallowing, the presence of gastrointestinal discomfort, and ghost pill effect.

Results: A total of 1,000 patients were enrolled. The majority had medium adherence to metformin 500 mg PR tablet (54%) and did not report swallowing difficulties (66.2%) due to its small size (64.4%) and oval shape (64.3%). The PR formulation of metformin was more acceptable than ER formulation due to no aftertaste (63%). The ghost pill effect was reported in 0.7% of patients with metformin 500 mg PR tablet against 8.5% with ER tablet. More than 60% of patients were "comfortable" (67.9%), had "much effect on their well-being" (61.8%), and were "satisfied" (69%) with metformin 500 mg PR tablet compared with ER tablet. Patient's dissatisfaction (42.7%) and taste (24.9%) were the common reasons cited by physicians and patients, respectively, for changing the treatment from metformin 500 mg ER to metformin 500 mg PR formulation. A total of 10 adverse events (nonserious) were reported, and all of them were resolved.

Conclusion: The technologically advanced formulation of metformin 500 mg PR tablets is more effective than that of metformin 500 mg ER tablets in improving adherence, compliance, satisfaction, and perception to medication in Indian patients with T2DM.

Keywords: abdominal discomfort, medication adherence, metformin prolonged release tablet, noncompliance, treatment satisfaction, type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is associated with significant morbidity and mortality worldwide.[1] In the last decade, high population growth rate, urbanization, and increase in average age of population have contributed significantly to the T2DM incidence.[2] As per International Diabetes Federation Atlas

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2017, the number of diabetes patients aged between 20 and 79 years is estimated to increase from 72.9 million (2017) to 134.3 million by 2045.[1]

Metformin, a biguanide antihyperglycemic drug, is prescribed in T2DM patients either as a monotherapy or in combination with sulfonylurea, dipeptidyl peptidase-4 inhibitor, or sodium-glucose cotransporter inhibitor in divided doses twice to thrice daily.[1,3,4] It is considered as the first-line pharmacologic treatment.[3] However, many patients cannot tolerate metformin in adequate amounts due to its gastrointestinal (GI) side effects such as nausea, vomiting, headache, diarrhea, stomach pain, increased flatulence, indigestion, abdominal discomfort, and loss of appetite along with metallic taste.[5] These side effects are considered as one of the major reasons for patient noncompliance and metformin discontinuation.[6] Hence, an extended-release (ER) formulation of metformin with once-daily dosage was developed to reduce the GI side effects and improve patient adherence to treatment.[7,8] However, metformin ER tablet was associated with a "ghost pill" effect; ie, an insoluble external shell of the pill is excreted intact in feces and serves as a source of anxiety and mistrust among patients and caregivers. This effect though does not hamper the drug absorption, or its efficacy should be handled in a sensitive manner.[9]

Abbott has recently developed a smaller sized metformin 500 mg prolonged release (PR) tablet containing metformin hydrochloride 500 mg (Gluformin I 500 mg), with the help of technological advancement, with the rationale to improve metformin ER formulation and enhance patient adherence to the prescribed regimen. The PR formulation of metformin 500 mg has sustained uniform drug release profile without the burst release phenomenon that is observed with metformin 500 mg ER formulation. This reduces GI irritation and improves patient satisfaction and medication adherence. The oval shape, small size, and specific coating (length: 13.99 mm; breadth: 8.99 mm, and height: 7.73 mm) of the tablet facilitate easy gliding of the tablet in the mouth, further increasing patient compliance. Although the metformin 500 mg PR tablet appears to have some added advantages over metformin 500 mg ER formulation, no clinical trials have been conducted yet to compare these formulations.

To the best of our knowledge, this is the first postmarketing observational study (using physician-approved validated questionnaire) to compare adherence, satisfaction, and experience with the technologically advanced formulation of metformin 500 mg PR tablet in comparison with metformin 500 mg ER tablet in Indian patients with T2DM.

Patients and methods

Patients

Patients with an established diagnosis of T2DM who were on a stable dose of metformin 500 mg PR tablet for at least 1 month and received metformin 500 mg ER tablets previously were enrolled in this prospective, single-visit, nonrandomized, postmarketing observational study. The patients were recruited from January 3, 2017, to September 15, 2017, from 50 sites across all four zones (north zone [Delhi]; west zone [Mumbai and Ahmedabad]; south zone [Hyderabad, Bangalore, and Kochi]; and east zone [Kolkata]) of India (Figure 1). The reason for the clinical decision to shift a patient from metformin 500 mg ER to metformin 500 mg PR tablets was not decided by the study protocol but was the sole discretion of the treating physician as a part of their practice judgment and was recorded in the case report form (CRF).

Both male and female patients aged between 18 and 60 years were considered eligible to participate in this study after signing the patient authorization form, which incorporated informed consent and allotted a unique identification number to maintain their privacy and confidentiality. Patients who had received any other oral hypoglycemic drugs, metformin combination therapy, or insulin within 3 months before screening were not included in the study. Additionally, patients who had a severe chronic GI problem; cardiac, hepatic, neurological, renal diseases or malignancies; exacerbation of chronic illnesses; or severe and acute infections; complicated infections or those participated in any other interventional trial within 30 days prior to screening were excluded from the study. Pregnant and lactating women or those unable to understand the study or provide answers to the questionnaire were also excluded from the study.

Data collection

The demographic details, medical/surgical/family history, vital signs, general physical examination, diagnosis and duration of T2DM treatment, details of concomitant illness, and medications and adverse events (AEs) were recorded in the CRF.

Patients' adherence, experience, and satisfaction with metformin 500 mg PR tablets for at least 1 month were assessed by the questionnaire (Table S1). This paper-based study questionnaire was prepared by six physicians (three from Hyderabad, two from Mumbai, and one from Bangalore) and evaluated the following five items—1) medication adherence, 2) reasons for noncompliance with metformin 500 mg

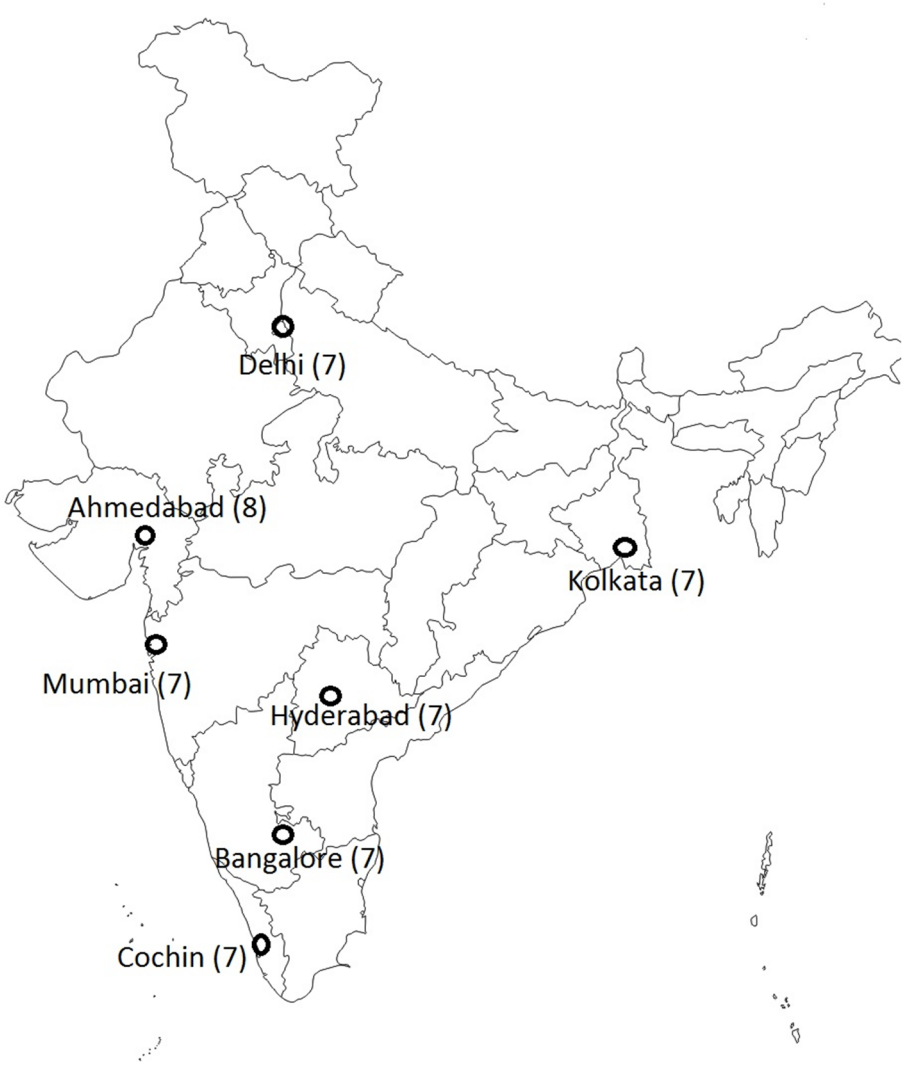

Figure 1 Site distribution.
Note: The number of sites is represented in parentheses.

ER tablets, 3) patient's experience and 4) satisfaction with metformin 500 mg PR tablets as compared with metformin 500 mg ER tablets, and 5) patient's preference of antidiabetic medication (metformin 500 mg PR or metformin 500 mg ER tablets). The study protocol and other related documents were approved by two independent ethics committees: CLINICOM independent ethics committee for sites at east and south zones and CONSCIENCE independent ethics committee for sites at north and west zones.

The study was conducted as per the guidelines of Declaration of Helsinki, International Council for Harmonization Good Clinical Practice standards, Indian Council of Medical Research, Indian GCP Guidelines, and the approved protocol.

Study assessment tools

Patient's adherence was assessed on the basis of an eight-item scale. A score >2 was considered as low adherence; a score between 1 and 2 was considered as medium adherence; and a score of 0 was considered as high adherence.

Patient's experience with metformin 500 mg PR tablets, as compared with metformin 500 mg ER tablets, was rated on a scale of 0–4 where scores are indicated as 0 = "strongly agree," 1 = "agree," 2 = "neither agree or disagree," 3 = "disagree," and 4 = "strongly disagree."

The symptoms of abdominal discomfort after taking metformin 500 mg PR tablets were rated on a scale of 0–4 where scores are indicated as 0 = "did not suffer at all," 1 = "suffered 1–2 times in past 2 weeks," 2 = "suffered 5–6 times

in past 2 weeks," 3 = "suffered 9–10 times in past 2 weeks," and 4 = "suffered most of the times."

The symptoms of abdominal discomfort after taking metformin 500 mg ER tablets were indicated as "yes" or "no."

The comfort level with metformin 500 mg PR tablets against metformin 500 mg ER tablets was rated on a scale of 0–4 where scores are indicated as 0 = "very comfortable," 1 = "comfortable," 2 = "neutral," 3 = "uncomfortable," and 4 = "very uncomfortable."

The effect of metformin 500 mg PR tablets on patient's well-being was compared with metformin 500 mg ER tablets on a scale of 0–4 where scores are indicated as 0 = "a great deal," 1 = "much," 2 = "somewhat," 3 "little," and 4 = "not much effect."

The level of satisfaction with metformin 500 mg PR tablets, compared with metformin 500 mg ER tablets, was rated on a scale of 0–4 where scores are indicated as 0 = "very satisfied," 1 = "satisfied," 2 = "neutral," 3 = "dissatisfied," and 4 = "very dissatisfied."

Study outcomes

The primary outcome of the study was to determine the proportion of patients with low, medium, and high adherence to metformin 500 mg PR tablets in the past 2 weeks (as indicated by the final score of question 1 of the patient questionnaire). The secondary outcomes were the proportion of patients 1) who rated metformin 500 mg PR against metformin 500 mg ER tablets when inquired about any feeling of discomfort while swallowing the tablet, ease of swallowing because of its size and shape, and acceptability due to no aftertaste; 2) who had nausea, vomiting, diarrhea, stomach pain, increased flatulence, and loss of appetite (symptoms under abdominal discomfort) when they were on metformin 500 mg PR tablets and metformin 500 mg ER tablets; 3) who experienced ghost pill effect with metformin 500 mg PR vs metformin 500 mg ER tablets; 4) who rated their comfort with metformin 500 mg PR tablets against metformin 500 mg ER tablets; 5) who rated their well-being with metformin 500 mg PR tablets against metformin 500 mg ER tablets; and 6) who rated their satisfaction with metformin 500 mg PR tablets against metformin 500 mg ER tablets.

Other additional study outcomes were physician-cited reasons for changing the antidiabetic medication from metformin 500 mg ER to metformin 500 mg PR tablets and patient-cited reasons for noncompliance when on metformin 500 mg ER tablets. The safety outcome of the study was to record the nature and frequency of AEs.

Statistical analysis

As this was a noninterventional study, no formal sample size calculation was done. To make sample size sufficiently large enough to estimate the proportion of treatment adherence to metformin 500 mg PR tablet at the level of precision ≤0.05, ~1,000 patients were planned to be enrolled in the study. The data obtained from the patients and physicians were summarized descriptively; the continuous variables were presented as mean ± SD and the categorical variables as frequencies and percentages. The statistical analysis was done using Statistical Analysis System® Version 9.4 software.

Results

Baseline characteristics

Of 1,000 enrolled patients, 548 were men and 452 were women. The mean age, body mass index, and waist circumference were 46.6±9.3 years, 26.5±4.3 kg/m^2, and 90.2±11.0 cm, respectively. The majority of the patients were married (94.7%), were graduates or postgraduates (47%), were semi-professionals (31%), had a monthly family income in the range of Rs 18,498–36,996 (39.1%), and belonged to upper-middle socioeconomic class (56.4%; Table 1).

A total of 380 patients had a family history of diabetes where >5% of the patients had their parents (28.4%) or immediate siblings (8.6%) as diabetic. More than 10% of the patients were associated with hypertension (26%) or dyslipidemia (13.3%) and were on either telmisartan (16.1%), rosuvastatin (10.4%), or atorvastatin (6.8%).

Diabetes-related complications were evident in <1% of the overall population. The vital signs (pulse and respiratory rate and diastolic blood pressure [BP]) were normal. The mean ± SD systolic BP and diastolic BP were 128.1±12.1 and 80.2±7.5 mmHg, respectively. The majority of the patients had normal findings on a physical examination.

Study outcomes

Of the 1,000 patients, the data of one patient was missing. A total of 999 (99.9%) subjects completed and signed the questionnaire. Table 2 summarizes the results of the study outcomes.

Primary outcome

The mean treatment adherence score was reported to be 2.64±1.71. Of the 1,000 patients, 44.5% had low adherence, 54% had medium adherence, and 1.4% had high adherence to metformin 500 mg PR tablets.

Table 1 Baseline characteristics

Parameter	Total number of patients (N=1,000)
Age (years), mean ± SD (range)	46.6±9.3 (19.0:67.0)
Men/women, n	548:452
Marital status, n	1,000
Married, n (%)	947 (94.7)
Single, n (%)	33 (3.3)
Divorced, n (%)	1 (0.1)
Widowed, n (%)	19 (1.9)
Weight (kg), n, mean ± SD (range)	999, 71.8±13.0 (39.0:171.0)
Height (m), n, mean ± SD (range)	999, 1.6±0.1 (1.4:1.9)
Body mass index (kg/m^2), n, mean ± SD (range)	999, 26.5±4.3 (14.6:52.7)
Waist circumference (cm), n, mean ± SD (range)	965, 90.2±11.0 (1.0:176.0)
Occupation, n	998
Profession, n (%)	164 (16.4)
Semi-profession, n (%)	310 (31.0)
Clerical, shop owner, farmer, n (%)	136 (13.6)
Skilled worker, n (%)	147 (14.7)
Semi-skilled worker, n (%)	64 (6.4)
Unskilled worker, n (%)	33 (3.3)
Unemployed, n (%)	144 (14.4)
Education, n	998
Profession or honors, n (%)	93 (9.3)
Graduate or postgraduate, n (%)	470 (47.0)
Intermediate or post-high school diploma, n (%)	213 (21.3)
High school certificate, n (%)	139 (13.9)
Middle school certificate, n (%)	52 (5.2)
Primary school certificate, n (%)	19 (1.9)
Illiterate	12 (1.2)
Monthly family income (Rs), n	998
≥36,997, n (%)	258 (25.8)
18,498–36,996, n (%)	391 (39.1)
13,874–18,497, n (%)	195 (19.5)
9,249–13,873, n (%)	92 (9.2)
5,547–9,248 n (%)	19 (1.9)
1,866–5,546, n (%)	13 (1.3)
≤1,865, n (%)	30 (3.0)
Socioeconomic status, n	998
Lower socioeconomic class (score <5), n (%)	22 (2.2)
Upper lower socioeconomic class (score 5–10), n (%)	73 (7.3)
Lower middle socioeconomic class (score 11–15), n (%)	185 (18.5)
Upper middle socioeconomic class (score 16–25), n (%)	564 (56.4)
Upper socioeconomic class (score 26–29), n (%)	154 (15.4)
Diabetes complications, n	985
Diabetic retinopathy, n (%)	3 (0.3)
Diabetic foot ulcer, n (%)	1 (0.1)
Diabetic ketoacidosis, n (%)	1 (0.1)
Peripheral vascular disease, n (%)	2 (0.2)
Diabetic nephropathy, n (%)	4 (0.4)
Diabetic neuropathy, n (%)	8 (0.8)
Erectile dysfunction, n (%)	5 (0.5)
Vital parameters, n	993
Pulse (beats/min), mean ± SD (range)	82.2±9 (60:115)
Respiratory rate (beats/min), mean ± SD (range)	17.9±2.3 (12:26)
Systolic blood pressure (mm/Hg), mean ± SD (range)	128.1±12.1 (100:190)
Diastolic blood pressure (mm/Hg), mean ± SD (range)	80.2±7.5 (40:120)

Note: n represents the number of patients analyzed in the study.

Table 2 Study outcomes

Parameters	Total number of patients (N=1,000)
Treatment adherence to metformin 500 mg PR tablet, n, mean ± SD (range)	999, 2.64±1.71 (0:7)
Low, n (%)	445 (44.50)
Medium, n (%)	540 (54.00)
High, n (%)	14 (1.40)
Details of any feeling of discomfort, for ease of swallowing because of its size and shape, for acceptability due to no aftertaste for metformin 500 mg PR tablet in comparison with metformin 500 mg ER tablet, n	999
I do not feel any discomfort while swallowing the metformin 500 mg PR tablet compared with metformin 500 mg ER tablet, n (%)	
Strongly agree	228 (22.80)
Agree	662 (66.20)
Neither agree or disagree	109 (10.90)
Disagree	0
Strongly disagree	0
Compared with metformin 500 mg ER tablet, metformin 500 mg PR tablet appears easy to swallow because of its size, n (%)	
Strongly agree	214 (21.40)
Agree	644 (64.40)
Neither agree or disagree	140 (14.00)
Disagree	1 (0.10)
Strongly disagree	0

Table 2 (*Continued*)

Parameters	Total number of patients (N=1,000)
Compared with metformin 500 mg ER tablet, metformin 500 mg PR tablet is easy to swallow because of its shape, n (%)	
Strongly agree	178 (17.80)
Agree	634 (63.40)
Neither agree or disagree	184 (18.40)
Disagree	2 (0.20)
Strongly disagree	1 (0.10)
Metformin 500 mg PR tablet is acceptable compared with metformin 500 mg ER tablet as there is no aftertaste, n (%)	
Strongly agree	186 (18.60)
Agree	630 (63.00)
Neither agree or disagree	183 (18.30)
Disagree	0
Strongly disagree	0
Details of each of the symptoms under abdominal discomfort for metformin 500 mg PR tablet, n	999
Nausea, n (%)	
Did not suffer at all	997 (99.70)
Suffered 1–2 times in the past 2 weeks	1 (0.10)
Suffered 5–6 times in the past 2 weeks	0
Suffered 9–10 times in the past 2 weeks	0
Suffered most of the times	1 (0.10)
Vomiting, n (%)	
Did not suffer at all	998 (99.80)
Suffered 1–2 times in the past 2 weeks	1 (0.10)
Suffered 5–6 times in the past 2 weeks	0
Suffered 9–10 times in the past 2 weeks	0
Suffered most of the times	0
Diarrhea, n (%)	
Did not suffer at all	996 (99.60)
Suffered 1–2 times in the past 2 weeks	3 (0.30)
Suffered 5–6 times in the past 2 weeks	0
Suffered 9–10 times in the past 2 weeks	0
Suffered most of the times	0
Stomach pain, n (%)	
Did not suffer at all	998 (99.80)
Suffered 1–2 times in the past 2 weeks	0
Suffered 5–6 times in the past 2 weeks	0
Suffered 9–10 times in the past 2 weeks	1 (0.1)
Suffered most of the times	0
Increased flatulence, n (%)	
Did not suffer at all	998 (99.80)
Suffered 1–2 times in the past 2 weeks	1 (0.10)
Suffered 5–6 times in the past 2 weeks	0
Suffered 9–10 times in the past 2 weeks	0
Suffered most of the times	0
Loss of appetite, n (%)	
Did not suffer at all	996 (99.60)
Suffered 1–2 times in the past 2 weeks	3 (0.30)
Suffered 5–6 times in the past 2 weeks	0
Suffered 9–10 times in the past 2 weeks	0
Suffered most of the times	0
Details of various symptoms of abdominal discomfort when on metformin 500 mg ER tablet, n	999
Nausea, n (%)	0
Vomiting, n (%)	0
Diarrhea, n (%)	1 (0.1)
Stomach pain, n (%)	0
Increased flatulence, n (%)	0
Loss of appetite, n (%)	0
Details of ghost pill effect with, n	993
Metformin 500 mg PR tablet, n (%)	7 (0.70)
Metformin 500 mg ER tablet, n (%)	85 (8.50)
Details of comfort with metformin 500 mg PR tablet as compared with metformin 500 mg ER, n	999
Compared with metformin 500 mg ER tablet, how comfortable are you with metformin 500 mg PR tablet? n (%)	
Very comfortable	224 (22.40)
Comfortable	679 (67.90)
Neutral	95 (9.50)
Uncomfortable	1 (0.10)
Very uncomfortable	0
Details of metformin 500 mg PR tablet on well-being as compared to metformin 500 mg ER, n	999
What is the effect of metformin 500 mg PR tablet on your well-being compared with metformin 500 mg ER tablets? n (%)	
A great deal	213 (21.30)
Much	618 (61.80)
Somewhat	146 (14.60)
Little	8 (0.80)
Not much	14 (1.40)
Details of satisfaction level with metformin 500 mg PR tablet as compared to metformin 500 mg ER tablet, n	999
How satisfied are you with metformin 500 mg PR tablet compared with metformin 500 mg ER tablet? n (%)	

Table 2 (*Continued*)

Parameters	Total number of patients (N=1,000)
Very satisfied	217 (21.70)
Satisfied	690 (69.00)
Neutral	91 (9.10)
Dissatisfied	1 (0.10)
Very dissatisfied	0
Details of reasons for switching to metformin 500 mg PR tablet from metformin 500 mg ER tablet, n	999
How satisfied are you with metformin 500 mg PR tablet compared with metformin 500 mg ER tablets? n (%)	
Patient had difficulty in swallowing because of the size of the earlier tablet	205 (20.50)
Patient had difficulty in swallowing due to the shape of the earlier tablet	233 (23.30)
Patient did not like the taste of the earlier medication	111 (11.10)
Ghost pill effect	83 (8.30)
Dissatisfaction with the earlier antidiabetic treatment	427 (42.70)
Patient had abdominal discomfort because of the earlier medication	70 (7.00)
Details of reasons cited by the patients for their noncompliance when on metformin 500 mg ER tablets, n	811
Size of the tablet, n (%)	214 (21.40)
Current medicine sticks in the throat (food pipe)	3 (0.30)
Generally find difficult to swallow medication	198 (19.80)
Very large and makes it uncomfortable to swallow	13 (1.30)
Do not like the taste of the medication, n (%)	249 (24.90)
Felt worse because of medication side effects, n (%)	1 (0.10)
Bloating	1 (0.10)
Dissatisfaction with antidiabetic medication, n (%)	109 (10.90)
Feeling tired of taking medicines daily	109 (10.90)
Other reasons, n (%)	238 (23.80)
Forgetfulness	131 (13.10)
Inconvenience or interference with daily activities	31 (3.10)
Lack of finance	2 (0.20)
Lack of time to comply with the medication regimen	13 (1.30)
Medicine not available with me during travel	35 (3.50)
Taking medicines upsets me as it reminds me of my disease	26 (2.60)

Abbreviations: ER, extended-release; PR, prolonged release.

Secondary outcomes

Ease of swallowing (because of its size and shape), acceptability (due to no aftertaste), comfort, patients' well-being, and satisfaction with metformin 500 mg PR tablets in comparison with metformin 500 mg ER tablets are the secondary outcomes of this study.

More than 60% of the patients reported "agreed" that they did not have any feeling of discomfort while swallowing the metformin 500 mg PR tablet (66.2%) as compared with metformin 500 mg ER tablets. Metformin 500 mg PR tablet was easier to swallow because of its size (64.4%) and shape (63.4%) and was considered as more acceptable than metformin 500 mg ER tablets due to its no aftertaste (63%).

The majority (67.9%) of the patients reported being "comfortable" followed by "very comfortable" (22.4%) with metformin 500 mg PR tablets in comparison with metformin 500 mg ER tablets. The majority (61.8%) of the patients reported a "much" effect followed by "a great deal" (21.3%) and a "somewhat" (14.6%) effect on their well-being after taking metformin 500 mg PR tablets as compared to metformin 500 mg ER tablets. More than three fourths (69%) of the patients reported being "satisfied" followed by "very satisfied" (21.7%) with metformin 500 mg PR tablets compared with metformin 500 mg ER tablets.

Abdominal discomfort

More than 99% of the patients on metformin 500 mg PR tablets reported that they "did not suffer at all" of any symptoms under abdominal discomfort, including nausea, vomiting, diarrhea, stomach pain, increased flatulence, and loss of appetite. In addition, none of the patients taking metformin 500 mg ER tablets experienced nausea, vomiting, stomach pain, increased flatulence, and loss of appetite. One patient experienced diarrhea on taking metformin 500 mg ER tablet.

Ghost pill effect

A higher proportion of patients experienced ghost pill effect with metformin 500 mg ER tablet compared with metformin 500 mg PR tablet (8.5% vs 0.7%).

Reasons cited by physicians for changing the antidiabetic medication from metformin 500 mg ER to metformin 500 mg PR tablets

The most common reason cited by physicians for changing the antidiabetic medication from metformin 500 mg ER to metformin 500 mg PR tablets was "patient dissatisfaction with the former treatment" (42.7%) followed by "difficulty

in swallowing metformin 500 mg ER tablet" due to its shape (23.3%) and size (20.5%).

Reasons cited by patients for their noncompliance when on metformin 500 mg ER tablets

More than 10% of the patients cited that the reason for their noncompliance with metformin 500 mg ER tablets was the dislike of the taste of the medication (24.9%), followed by difficulty in swallowing due to its size (19.8%), their forgetfulness (13.1%), and feeling of tiredness in taking the medication daily (10.9%).

Safety outcome

In total, ten AEs were reported during the study which included diarrhea, abdominal pain, decreased appetite, flatulence, nausea, vomiting, and head discomfort. All the AEs were nonserious and were resolved.

Discussion

Metformin is the most commonly prescribed drug in patients with T2DM and has been in clinical use for decades.[3] Over the last 15 years, it has been used successfully as the first-line therapy in patients with T2DM, largely as immediate-release formulation requiring two or three times daily dosing.[6] Despite its clinical benefits, up to 25% of patients suffer from metformin-associated GI side effects, with ~5% unable to tolerate in adequate amounts.[10] These side effects may reduce compliance with metformin and cause treatment dissatisfaction among the users. Hence, once-daily ER formulation of metformin was developed, which improved GI tolerability and patient adherence to treatment. However, the excretion of nondisintegrated insoluble external shell with ER formulation "as a ghost pill" increased the anxiety and mistrust among patients.[9] Therefore, Abbott developed the technologically advanced formulation of metformin 500 mg PR tablet that is small in size and oval in shape and releases metformin uniformly without any burst release. This drug was expected to reduce GI-related side effects and improve patient satisfaction and treatment adherence. In the present study, we have compared medication adherence, patient satisfaction, and overall experience with metformin 500 mg PR tablet against metformin 500 mg ER tablet, using a self-validated physician-approved questionnaire.

More than 50% of our patients had medium adherence to metformin 500 mg PR tablets (54%). In addition,>60% of the patients were comfortable (67.9%) and satisfied (69%), had no feeling of discomfort after swallowing (66.2%), felt easy to swallow owing to its small size (64.4%) and oval shape (63.4%), and had higher acceptability to metformin 500 mg PR tablets due to its no aftertaste (63%). The most frequent reason for changing metformin 500 mg ER to metformin 500 mg PR regimen was treatment dissatisfaction (42.7%) followed by difficulty in swallowing the former antidiabetic tablet due to its shape (23.3%) and size (20.5%). Hence, the improved tablet design of metformin 500 mg PR tablets in terms of small size and oval shape (length: 13.99 mm; breadth: 8.99 mm, and height: 7.73 mm), no aftertaste, and hydrophilic matrix enhanced the swallowing of medication. This helped in good patient adherence and compliance with metformin 500 mg PR tablets as compared to metformin 500 mg ER tablets.

Our results were in corroboration with the previous literature where therapy-related factors, including treatment complexity; duration of treatment period; medication side effects; taste of medication; and size, shape, and ease-of-swallowing of tablets tend to affect patient compliance and treatment adherence.[11] A quantitative survey in 400 adults receiving valproate tablets for the past 6 months showed that approximately more than half (65.8%) of patients were "very interested" in medications that were easier to swallow.[12] Studies in adults suggest that increased size of tablets, >~8 mm in diameter, is associated with more patient complaints related to swallowing difficulties and therefore reduces treatment compliance.[13,14]

The difficulty in swallowing tablets is a problem in around 16 million people in the USA.[15] Of those who have trouble swallowing medications, around 8% skip the dose of prescribed medication, and 4% discontinued therapy because of the tablets.[16] Importantly, such individuals who find it difficult to swallow tablets frequently cite the size as the main reason for the difficulty in swallowing.[16] For any given size, certain shapes may be easier to swallow than others. Studies have suggested that oval tablets may be easier to swallow with faster esophageal transit times than round tablets of the same weight.[17] In 2001, Overgaard et al investigated the swallowability and the patient preferences of tablets with different sizes and shapes and revealed that the ideal tablet should be small and circular. The oval shape should be preferred if the amount of drug requires bigger tablet.[18]

The forgetfulness, financial constraints and feeling of being well have been considered as the common reasons behind noncompliance with antidiabetic drugs.[19,20] However, in our study, forgetfulness was cited by 13.1% patients, while financial constraints and interference with daily activities were reported by 0.2% and 3.1% patients, respectively, with metformin 500 mg ER tablets. The low proportion of patients

reporting such reasons may be due to a once-daily dose regimen, good tolerability, and low cost of metformin 500 mg ER tablets, which had improved patient compliance and treatment adherence. However, the big size of the tablet and aftertaste of medication were the two main reasons cited for patient's noncompliance with metformin 500 mg ER tablets.

In this study, nearly all the patients using metformin 500 mg PR tablet reported that they do not suffer from any of the abdominal symptoms, viz. abdominal discomfort, nausea, vomiting, diarrhea, stomach pain, increased flatulence, and loss of appetite. Better tolerability with metformin 500 mg PR tablet may be due to improved tablet design, which releases metformin into upper intestine by diffusion from a dual hydrophilic polymer matrix. This feature helps to provide slower, smoother, and longer gastric residence time of metformin 500 mg PR tablet, without an initial rapid rise in plasma metformin (GelShield diffusion system). The results of this study were in agreement with the published literature in reporting fewer GI side effects with the use of once-daily metformin PR formulation than that of immediate-release metformin.[21,22]

Furthermore, we noted that the incidence of ghost pill effect was ~12 times lower with metformin 500 mg PR formulation as compared to metformin 500 mg ER formulation (8.5% vs 0.7%). This change in tablet formulation has helped in better acceptability and confidence among patients and diabetologists treating such patients.[23] In our study, nearly 8.3% of patients switched from metformin ER tablets to metformin 500 mg PR formulation due to the ghost pill effect of the former treatment.

Our study has few strengths and limitations. This is the first study that highlights the adherence, satisfaction, and experience with metformin 500 mg PR tablet in Indian patients with T2DM. Second, patients were recruited during a regular visit to their general practitioner ensuring homogeneity in sociodemographic variables. Third, the questionnaire was developed and validated by six doctors who are subject matter experts. Fourth, it was a Pan-India study covering 50 sites across India. Last, patients provided the quantitative responses to the questions captured in the questionnaire. However, there were also few limitations in the study. First, it was an open-label observational study which limited the viability of our results, so confounding factors affecting its outcomes cannot be excluded. Second, it was a single-visit study without any prospective follow-up, which limited the evaluation of metformin 500 mg PR tablets over a longer period of time. Third, there was no correlation of adherence, satisfaction, and experience of treatment with different sociodemographic factors and other patient characteristics. Fourth, there was a high probability of overreporting as the questionnaire captured all patient-reported responses. Nevertheless, this study was the first attempt to explore the benefits of metformin 500 mg PR tablet in terms of adherence, satisfaction, and experience among the patients with T2DM in India.

Conclusion

The smaller size, oval shape, no aftertaste after swallowing, and decreased incidence of ghost pill effect have improved patient adherence and satisfaction of metformin 500 mg PR tablet in T2DM management. The PR feature offers multiple advantages over the traditional formulations due to better drug delivery that increases subject acceptability, ease of administration, and compliance. Improved patient adherence, satisfaction, and well-being along with marked reduction in GI side effects led to the metformin 500 mg PR tablets being preferred in a majority of T2DM patients for use in routine clinical practice. This formulation has the potential to improve compliance and long-term health outcomes in patients with T2DM. However, its efficacy and safety should be compared with other antidiabetic drugs in large clinical trials to evaluate and justify the role of metformin 500 mg PR tablets in the management of T2DM.

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Disclosure

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References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th ed. Brussels: International Diabetes Federation; 2017. http://www.diabetesatlas.org. Accessed October 7, 2018.
2. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. *Australas Med J*. 2014;7(1):45–48.
3. American Diabetes Association. Standards of medical care in Diabetes-2017: summary of revisions. *Diabetes Care*. 2017;40(Suppl 1):S4–S5.
4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2017 executive summary. *Endocr Pract*. 2017;23(2):207–238.
5. Bonnet F, Scheen A. Understanding and overcoming metformin gastrointestinal intolerance. *Diabetes Obes Metab*. 2017;19(4):473–481.

6. Kim CH, Han KA, Oh HJ, et al. Safety, tolerability, and efficacy of metformin extended-release oral antidiabetic therapy in patients with type 2 diabetes: an observational trial in Asia. *J Diabetes*. 2012;4(4):395–406.
7. Jabbour S, Ziring B. Advantages of extended-release metformin in patients with type 2 diabetes mellitus. *Postgrad Med*. 2011;123(1):15–23.
8. Levy J, Cobas RA, Gomes MB. Assessment of efficacy and tolerability of once-daily extended release metformin in patients with type 2 diabetes mellitus. *Diabetol Metab Syndr*. 2010;2(1):16.
9. Tungaraza TE, Talapan-Manikoth P, Jenkins R. Curse of The ghost pills: the role of oral controlled-release formulations in the passage of empty intact shells in faeces. Two case reports and a literature review relevant to psychiatry. *Ther Adv Drug Saf*. 2013;4(2):63–71.
10. Dujic T, Zhou K, Donnelly LA, Tavendale R, Palmer CNA, Pearson ER. Association of organic cation transporter 1 with intolerance to metformin in type 2 diabetes: a GoDARTS study. *Diabetes*. 2015;64(5):1786–1793.
11. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4(1):269–286.
12. Bhosle M, Benner JS, Dekoven M, Shelton J. Difficult to swallow: patient preferences for alternative valproate pharmaceutical formulations. *Patient Prefer Adherence*. 2009;3(3):161–171.
13. Channer KS, Virjee JP. The effect of size and shape of tablets on their esophageal transit. *J Clin Pharmacol*. 1986;26(2):141–146.
14. Liu F, Ranmal S, Batchelor HK, et al. Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations. *Drugs*. 2014;74(16):1871–1889.
15. ECRI Health Technology Assessment Group. Diagnosis and treatment of swallowing disorders (dysphagia) in acute-care stroke patients. *Evid Rep Technol Assess (Summ)*. 1999;(8):1–6.
16. Harris Interactive Inc. *Pill-Swallowing Problems in America: A National Survey of Adults*. New York, NY: Harris Interactive Inc. for Schwarz Pharma; 2003:1–39.
17. Hey H, Jørgensen F, Sørensen K, Hasselbalch H, Wamberg T. Oesophageal transit of six commonly used tablets and capsules. *Br Med J*. 1982;285(6356):1717–1719.
18. Overgaard AB, Højsted J, Hansen R, Møller-Sonnergaard J, Christrup LL. Patients' evaluation of shape, size and colour of solid dosage forms. *Pharm World Sci*. 2001;23(5):185–188.
19. Mukherjee S, Sharmasarkar B, Das KK, Bhattacharyya A, Deb A. Compliance to anti-diabetic drugs: observations from the diabetic clinic of a medical college in Kolkata, India. *J Clin Diagn Res*. 2013;7(4):661–665.
20. Pascal I, Ofoedu J, Uchenna N, Nkwa A, Uchamma GU. Blood glucose control and medication adherence among adult type 2 diabetic Nigerians attending a primary care clinic in under-resourced environment of Eastern Nigeria. *N Am J Med Sci*. 2012;4(7):310–315.
21. Davidson J, Howlett H. New prolonged-release metformin improves gastrointestinal tolerability. *Br J Diabetes Vasc Dis*. 2004;4(4):273–277.
22. Derosa G, D'Angelo A, Romano D, Maffioli P. Effects of metformin extended release compared to immediate release formula on glycemic control and glycemic variability in patients with type 2 diabetes. *Drug Des Devel Ther*. 2017;11:1481–1488.
23. Kandi M, Sivasai G, Rathnanand M, Reddy MS, Bhasker KV. Novel intervention to improve adherence to medication in diabetic patients: formulation and evaluation of metformin HCL novel dosage form. *Int J Pharm Sci*. 2013;5:587–592.

Supplementary material

Table S1 Patient questionnaire

Adherence to metformin 500 mg PR tablet based on the past 2 weeks	
Do you sometimes forget to take your pills?	☐ Yes ☐ No
People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your medicine?	☐ Yes ☐ No
Have you ever cut back or stopped taking your medicine without telling your doctor because you felt worse when you took it?	☐ Yes ☐ No
When you travel or leave home, do you sometimes forget to bring along your medicine?	☐ Yes ☐ No
Did you take all your medicines yesterday?	☐ Yes ☐ No
When you feel like your symptoms are under control, do you sometimes stop taking your medicine?	☐ Yes ☐ No
Taking medicine every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?	☐ Yes ☐ No
How often do you have difficulty remembering to take all your medicine?	☐ A. Never/rarely ☐ B. Once in a while ☐ C. Sometimes ☐ D. Usually ☐ E. All the time
Reasons for noncompliance when on metformin 500 mg ER tablets (Multiple choices can be ticked, and tick circles for exact reason.)	
☐ Size of the tablet ○ Very large and makes it uncomfortable to swallow ○ Generally find difficult to swallow medication ○ Current medicine sticks in the throat (food pipe) ☐ Don't like the taste of the medication ☐ Felt worse because of medication side effects ○ Bloating ○ Nausea ○ Diarrhea ○ Vomiting ○ Abdominal pain ○ Any other, specify:_____ ☐ Dissatisfaction with antidiabetic medication ○ Feeling tired of taking medicines daily Any other, specify: _____ ☐ Other reasons ○ Forgetfulness ○ Lack of time to comply with the medication regimen ○ Inconvenience or interference with daily activities ○ Lack of finance ○ Medicine not available with me during travel ○ Taking medicines upsets me as it reminds me of my disease ○ Any other, specify: _____	
Experience with metformin 500 mg PR tablet compared with metformin 500 mg ER tablet (Tick only one option per question.)	
I do not feel any discomfort while swallowing the metformin 500 mg PR tablet compared with metformin 500 mg ER tablet (Rate the medication based on the ease and comfort of swallowing.)	☐ 0 = Strongly agree ☐ 1 = Agree ☐ 2 = Neither agree or disagree ☐ 3 = *Disagree ☐ 4 = *Strongly disagree

(*Continued*)

Table S1 (*Continued*)

Adherence to metformin 500 mg PR tablet based on the past 2 weeks	
Compared with metformin 500 mg ER tablet, metformin 500 mg PR tablet appears easy to swallow because of its size	☐ 0 = Strongly agree ☐ 1 = Agree ☐ 2 = Neither agree or disagree ☐ 3 = Disagree ☐ 4 = Strongly disagree
Compared with metformin 500 mg ER tablet, metformin 500 mg PR tablet is easy to swallow because of its shape	☐ 0 = Strongly agree ☐ 1 = Agree ☐ 2 = Neither agree or disagree ☐ 3 = Disagree ☐ 4 = Strongly disagree
Metformin 500 mg PR tablet is acceptable compared with metformin 500 mg ER tablet as there is no aftertaste	☐ 0 = Strongly agree ☐ 1 = Agree ☐ 2 = Neither agree or disagree ☐ 3 = Disagree ☐ 4 = Strongly disagree

Do you experience any of the below-mentioned symptoms of abdominal discomfort after taking the Metformin 500 mg tablet? Please tick appropriate option for each symptom.

Symptoms of abdominal discomfort	0 = Did not suffer at all	1 = Suffered 1–2 times in the past 2 weeks	2 = Suffered 5–6 times in the past 2 weeks	3 = Suffered 9–10 times in the past 2 weeks	4 = Suffered most of the times
Nausea	☐	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐	☐
Diarrhea	☐	☐	☐	☐	☐
Stomach pain	☐	☐	☐	☐	☐
Increased flatulence	☐	☐	☐	☐	☐
Loss of appetite	☐	☐	☐	☐	☐

Did you experience any of the below-mentioned symptoms of abdominal discomfort while taking metformin 500 mg ER tablet?

- ○ Nausea ☐ Yes ☐ No
- ○ Vomiting ☐ Yes ☐ No
- ○ Diarrhea ☐ Yes ☐ No
- ○ Stomach pain ☐ Yes ☐ No
- ○ Increased flatulence ☐ Yes ☐ No
- ○ Loss of appetite ☐ Yes ☐ No

Do you see the tablet being excreted in the faeces/stools?

- ○ With metformin 500 mg PR tablet ☐ Yes ☐ No
- ○ With metformin 500 mg ER tablet ☐ Yes ☐ No

Satisfaction with metformin 500 mg PR tablet compared with metformin 500 mg ER formulation: (Tick only one option per question.)

Compared with metformin 500 mg ER tablet, how comfortable are you with metformin 500 mg PR tablet?	☐ 0 = Very comfortable ☐ 1 = Comfortable ☐ 2 = Neutral ☐ 3 = Uncomfortable ☐ 4 = Very uncomfortable
What is the effect of metformin 500 mg PR tablet on your well-being compared with metformin 500 mg ER tablets?	☐ 0 = A great deal ☐ 1 = Much ☐ 2 = Somewhat ☐ 3 = Little ☐ 4 = Not much

(*Contiued*)

Table S1 (*Continued*)

Adherence to metformin 500 mg PR tablet based on the past 2 weeks	
How satisfied are you with metformin 500 mg PR tablet compared with metformin 500 mg ER tablets? (based on how much your experience with the medication matches with your expectations)	☐ 0 = Very satisfied ☐ 1 = Satisfied ☐ 2 = Neutral ☐ 3 = Dissatisfied ☐ 4 = Very dissatisfied
Preference of antidiabetic medication (Tick one.)	
Metformin 500 mg PR tablet ☐ Metformin 500 mg ER tablet ☐	

Note: *To be reported to Abbott Pharmacovigilance within 24 hours via email as per protocol using the appropriate Orange form only for Abbott products.
Abbreviations: ER, extended-release; PR, prolonged release.