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Reducing the burden of diabetes treatment: A review of low-cost oral hypoglycemic medications

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Abstract

Background.—The vast majority of individuals diagnosed with diabetes are low/middle income and may have access to only three of the 11 oral hypoglycemic medications (OHMs) due to cost: metformin intermediate release (IR) or extended release (ER), sulfonylureas (glimepiride, glipizide, glyburide), and pioglitazone. Sulfonylureas and pioglitazone have had significant controversy related to potential adverse events, but it remains unclear whether these negative outcomes are class-, drug-, or dose-related.

Objective.—We conducted a narrative review of low-cost OHMs.

Methods.—We evaluated the maximum recommended (MAX) compared to the most effective (EFF) daily dose, time-to-peak change in HbA1c levels, and adverse events of low-cost oral hypoglycemic medications.

Results.—We found that the MAX was often greater than the EFF: metformin IR/ER (MAX: 2,550/2,000 mg, EFF: 1,500–2,000/1,500–2,000 mg), glipizide IR/ER (MAX: 40/20 mg, EFF: 20/5 mg), glyburide (MAX: 20 mg, EFF: 2.5–5.0 mg), pioglitazone (MAX: 45 mg, EFF: 45 mg). Time-to-peak change in HbA1c levels occurred at weeks 12–20 (sulfonylureas), 25–39 (metformin), and 25 (pioglitazone). Glimepiride was not associated with weight gain, hypoglycemia, or negative cardiovascular events relative to other sulfonylureas. Cardiovascular event rates did not increase with lower glyburide doses ($p<0.05$). Glimepiride and pioglitazone have been successfully used in renal impairment.

Conclusions.—Metformin, glimepiride, and pioglitazone are safe and efficacious OHMs. Prescribing at the EFF rather than the MAX may avoid negative dose-related outcomes. OHMs should be evaluated as individual drugs, not generalized as a class, due to different dosing and adverse-event profiles; Glimepiride is the preferred sulfonylurea since it is not associated with the adverse events as others in its class.

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Keywords

diabetes; medication; low-income or underserved; hypoglycemic medication; metformin; sulfonylurea; thiazolidinediones

INTRODUCTION

Diabetes is a major source of morbidity and mortality worldwide and has a strong association with poverty.[1] Of the 425 million people living with diabetes, the majority (80%) reside in low- or middle-income countries.[2] In high-income countries most (67%) individuals diagnosed with diabetes are from low- or middle-income socioeconomic communities.[3] Of the 11 oral hypoglycemic medications (OHMs), three are available at low-cost (<$10/month) in the US (metformin, sulfonylureas, thiazolidinediones (pioglitazone]).[1] The other eight classes (alpha-glucosidase inhibitors, amylin analogs, bile acid sequestrants, quick-release dopamine-2 agonists, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists, meglitinides, sodium-glucose Cotransporter (SGLT)-2 inhibitors) average $570/month ($6,840/year).[1] These data reveal that the vast majority of individuals diagnosed with diabetes may have access to only three low-cost options for OHM therapy. Sulfonylureas and pioglitazone have had substantial controversy regarding adverse events[4–6], but it is not clear whether these negative outcomes are class-, drug-, or dose-related.

Diabetes is associated with tremendous individual and system burdens, largely due to increasing costs of insulins and most OHM options.[1,7] Physician prescribing practices lack of transparent insurance rebate and discount pricing, and limited to no payer price negotiations have led to surging hypoglycemic medications costs in the US ($10 to $22 billion, 2002 to 2012).[7] In recent years there has been a paradigm shift of more international organizations recommending multiple OHMs regimens, treating even markedly elevated hemoglobin (Hb)A1c levels (>9%).[1,8–10] However beyond metformin as a first-line therapy, there has been significant controversy in deciding the most appropriate subsequent OHM.[1,8–10] Concerns for low-cost OHMs including the sulfonylureas and thiazolidinediones have related to potential adverse events (i.e., beta-cell loss, hypoglycemia, negative cardiovascular effects).[5,10,11] Strong evidence also suggests that pharmaceutical companies have influenced the discussion regarding therapeutics.[12] This may have contributed to less attention to older, low-cost OHMs and resulted in few residual options for many individuals and major public health burdens.[5,8]

In spite of substantial diversity of OHMs within a class[5,13,14], there is a paucity of data comparing these drugs individually. Additionally, low-cost OHM studies have had a diversity of methodology including dosing, adverse events, and duration of therapy. Further, though the maximum recommended daily dose (MAX) is established for OHMs[1,15,16], the most effective daily dose (EFF) is not, making it difficult to decipher whether adverse events would decrease or be eliminated if appropriate doses were used. These factors hinder the ability to conduct a robust systematic review or meta-analysis comparing individual OHMs within classes.

METHODS

In this study, we conducted a narrative review of low-cost OHMs by searching PubMed (until June 2019) for randomized controlled trials, systematic reviews, metanalyses, and observational studies that evaluated the MAX, EFF, time-to-peak change in HbA1c level, and adverse events associated with metformin (intermediate release (IR), extended release (ER)), sulfonylureas (glyburide, glipizide, glimepiride), and thiazolidinediones (pioglitazone). We structured the review using the PICOS model: participants (individuals with type 2 diabetes), intervention (OHM), comparison (OHMs-individually and by class), outcomes (MAX, EFF, HbA1c, adverse events), and study design (randomized, observational, systematic review, meta-analysis).[17]

RESULTS

Diabetes medication therapy is costly, placing many individuals at risk for suboptimal or no treatment. SGLT2 inhibitors and GLP-1 receptor agonists are among the most expensive ($399/month and $711/month, respectively).[1] Most insulins are also not available at low-cost (mean: $265/month).[1] The Prospective Urban Rural Epidemiology study (N=156,625; 110,803 households in 22 countries) revealed that insulin was available in 93.8% of pharmacies in high-income countries, differing from rates in middle-income (40.2%) and low-income (10.3%) countries.[18] Additionally, 63% of households in low-income countries could not afford insulin.[18]

NPH, Regular, and 70/30 insulin are available at a lower cost ($25/vial) from limited US pharmaceutical companies, but this may still be very expensive. For example, an individual prescribed 50 units of insulin twice daily would spend $75/month ($900/year) even at this reduced price. Also, unlike OHMs where cost is typically a reflection of the number of pills rather than an increase in dose, insulin prices escalate with higher levels. For instance, 30 tablets of metformin 500 mg/day are the same cost as 30 tablets of metformin 1000mg/day, whereas insulin NPH 50 units/day is twice as much as 25 units/day. Furthermore, additional costs of insulin supplies for self-monitoring and syringes make annual expenditures more than $2,000.[19]

Insulin concerns—In addition to cost-barriers associated with insulin, patient and system burdens are substantial.[20] Hypoglycemia has been associated with lower income and less education.[21] OHMs are reportedly as efficacious as insulin in treating severe uncontrolled diabetes (HbA1c >11%, insulin: −5.1%, OHMs: −4.6%, p=0.846) and with less system burden.[22] US national statistics have attributed nearly 100,000 annual emergency room visits to insulin-related issues.[23] Needle phobia and negative patient perceptions have resulted in increased non-adherence.[24]

Biguanides (metformin)

In concurrence with lifestyle modifications, metformin is clearly the recommended first-line therapy in type 2 diabetes.[1,8,9] Metformin reduces hepatic gluconeogenesis, increases skeletal muscle glucose uptake, suppresses lipogenic enzymes, and induces fatty acid oxidation, all of which positively effect both glycemic and lipid control.[25] There are two

formulations of metformin: immediate release (IR) and extended release (ER or XL). Metformin ER is now offered at prices comparable to IR, and both have similar effects on glycemic control.[1,26,27] However, the median time to reach peak plasma concentration is longer for ER (3 hours vs. 7 hours, respectively),[28] which may reduce the frequency of gastrointestinal side effects and thus improve adherence.[29,30] One study found that patients prescribed metformin ER had better adherence than those taking IR (80% vs. 72%, $p=0.0026$), and those switched from IR to ER exhibited improved adherence (62% to 81%, $p<0.0001$) and glycemic control (HbA1c: 9.1% to 8.4%).[29]

Maximum recommended (MAX) and most effective (EFF) dosing.—Metformin IR/ER is initiated at 500 mg or 850 mg daily, increased in 500 mg/day increments weekly, and has a maximum dose of 2,550 mg/day (ER: 2,000 mg/day).[1,31] A clinical trial (N=451) that evaluated metformin 500–2,500 mg in 500-mg increments found a linear dose response for HbA1c improvement (500 mg: −0.6% to 2,000 mg: −2.0%) and that each 500-mg increment increase was significant until 2,000 mg/day ($p<0.05$).[32] Although the MAX is 2,550 mg/day, studies have shown that the EFF is between 1,500–2,000 mg/day.[32,33] Metformin has been shown to improve glycemic control linearly at least until 25–39 weeks,[27,33] but further studies are needed beyond this timeframe to verify time-to-peak HbA1c effects.

Adverse events.—Adverse-event profiles are similar for metformin IR and ER, most commonly involving gastrointestinal effects (abdominal pain, decreased appetite, diarrhea, heartburn, flatulence, nausea, and vomiting).[26,27] However, the ER formulation is associated with fewer gastrointestinal effects due to slower absorption and therefore delayed maximum plasma concentration.[30] These effects may play a role in weight loss associated with metformin (7% loss of total body weight).[34]

Other adverse events have been linked to B12 deficiency and negative metabolic effects. Although not entirely clear, B12 deficiency in metformin users may be related to dietary and enterohepatic absorption as well as proton pump inhibitor use.[35–37] It is now recommended to test B12 levels in patients prescribed metformin.[1,9,35] Metformin use is contraindicated for patients with increased risk of lactic acidosis (i.e., renal impairment), but if prescribed appropriately dose, this risk approaches zero.[31,38] Prior guidelines recommended against metformin use if creatinine levels were elevated (men: 1.5 mg/dL; women: 1.4 mg/dL), but it is now contraindicated based on glomerular filtration rate (<30 mL/min/1.73 m^2).[38] Although there have been concerns related to its use in patients with liver disease and congestive heart failure, metformin has been shown to reduce all-cause mortality in patients with moderate liver and heart disease.[39]

Sulfonylureas

Sulfonylureas are the oldest class of OHMs, emerging in 1942. Although they constitute a single class, they differ in terms of receptors and binding sites (SUR1, SUR2A; A, B; respectively) on pancreatic beta-cells, route of elimination, duration of action, and rate of absorption.[40] Sulfonylureas stimulate insulin secretion by pancreatic beta-cells and decrease hepatic insulin clearance;[40] thus, their efficacy depends on functioning beta-cells.[40]

Although a shorter duration of diabetes may be suggestive of sulfonylurea efficacy, individual variations in glycemic control over time would make this difficult to determine. Although glipizide and glimepiride metabolites are renally excreted, they exhibit less hypoglycemic activity than glyburide and are therefore more frequently used in patients with renal impairment.[40]

The seven sulfonylureas can be categorized into two generations (first-generation: chlorpropamide, tolbutamide; second-generation: glipizide, gliclazide, gliquidone, glimepiride, glyburide/glibenclamide).[40] For the purposes of this review, the most common clinically used second-generation drugs are reviewed.

Glyburide (glibenclamide).—Glyburide is initiated at a dose of 2.5–5 mg and has a MAX of 20 mg/day.[1,20] Although the MAX is 20 mg/day,[1] studies have failed to demonstrate efficacy at this dose. One study found no improvement in fasting glucose levels beyond 2.5 mg/day to 5 mg/day and reported no effect on insulin stimulation beyond 5 mg/day (2 mg: 51.4%; 5 mg: 58.3%; 10 mg: 44.4%; 20 mg: 33.5%).[41,42] Another study found that increasing glyburide from 10 to 20 mg/day did not significantly affect HbA1c ($p=0.08$), but lower doses were not evaluated.[43] There are limited data on glyburide's effect on HbA1c prior to 12 weeks. However, a systematic review showed that HbA1c changed −1.1% to −1.2% between 12–20 weeks but did not improve thereafter.[15,33,44] Since studies titrated sulfonylureas to achieve glycemic goals, data are limited to compare various doses over time.

Glipizide.—Glipizide is available in IR and ER (extended/sustained/controlled release). These formulations do not differ in terms of HbA1c reduction, but the controlled release formulation has shown lower C-peptide ($p<0.05$) and fasting insulin ($p<0.01$) levels compared to the IR formulation.[45] Glipizide IR/ER are initiated at 5 mg/day.[1,38] Glipizide IR's MAX is 40 mg/day but had an EFF of 20 mg/day in a 10–40 mg/day evaluation.[43] Glipizide ER's MAX is 20 mg/day, but a 16-week investigation of 5–60 mg/day doses determined the EFF to be 5 mg/day.[46] Data suggest that glipizide reduces HbA1c (−0.9% to −1.8%), and time-to-peak HbA1c change occurs by 16 weeks,[46,47] although further studies are needed beyond this timeframe to make definitive conclusions.

Glimepiride.—Glimepiride is initiated at 1–2 mg/day and has a MAX of 8 mg.[1,11,48] A 14-week study (N=304) revealed that glimepiride exhibits dose-related responses at 2–8 mg/day, although there are small HbA1c differences between 4 and 8 mg/day (−1.8% vs. −1.9%, respectively).[49] No significant differences in glycemic control have been demonstrated beyond 8 mg daily.[48] The time-to-peak HbA1c reduction (−1.0% to −1.9%) is 12–14 weeks.[44]

Adverse events.—Concerns regarding adverse events associated with sulfonylureas were recently highlighted.[5,50,51] However, sulfonylureas are generally well tolerated, and growing evidence has shown that adverse events vary by drug and should not be generalized to the class.[5,11,40] Several studies evaluating only glyburide or a first-generation medication have attributed adverse events to the entire class of sulfonylureas.[15,50–52]

Beta-cell loss.—Potential lack of beta-cell preservation or expedition of their failure are concerns related to this class though investigations often do not delineate differences between individual sulfonlyureas.[40] In vitro, glyburide has been associated with substantially greater damage to islet cells compared to glimepiride and glipizide.[11] Sulfonylureas are routinely prescribed at doses higher than their EFF[43], and this practice may expedite beta cell loss.

Cardiovascular.: In the setting of diabetes, some sulfonylureas have been found to inhibit K_{ATP} channels in cardiac monocytes, resulting in ischemic preconditioning inhibition.[53] Glyburide has more affinity for cardiac monocytes than glipizide and glimepiride.[5] This provides an explanation for the negative cardiovascular outcomes seen with glyburide.[53] It is important to note, however, that negative cardiovascular outcomes have not been demonstrated with glyburide doses ≤10 mg/day, which is above its highest EFF (2.5–5 mg/day).[4,41,42] Among 14,213 new users of glyburide or gliclazide, major adverse cardiovascular events were evident in patients taking high (>10 mg/day) but not low (≤10 mg/day) doses.[4] This may have provided a rationale for a meta-analysis of randomized controlled trials that did not find an increase in all-cause mortality, myocardial infarction, or cardiovascular mortality associated with glyburide, glimepiride, or glipizide.[54]

Weight gain.: A study of glipizide ER at doses ranging from 5 to 60 mg/day did not observe patient weight gain, regardless of dose.[46] Glimepiride demonstrated a dose-related weight gain at 1-, 4-, and 8-mg doses (0.0 kg, 0.5 kg, and 0.9 kg, respectively) compared to placebo (−1.82 kg) in one study.[49] Another study found glimepiride to have neutral effects on weight or to induce weight loss.[55] The latter findings were attributed to extra-pancreatic, glucose-lowering effects, including increased peripheral glucose uptake and decreased endogenous glucose production.[55] Another review reported weight gain; however, sulfonylureas were generalized as a class, making it difficult to delineate individual drug effects.[40] Furthermore, the average weight gain associated with sulfonylureas (2 kg) was lower than that associated with insulin (4 kg).[40]

Hypoglycemia.: Hypoglycemic effects are markedly greater with glyburide compared to glipizide and glimepiride, particularly in certain populations (those with renal impairment and the elderly).[5] Patients taking glyburide have been shown to exhibit delayed plasma glucose recovery compared to controls (p=0.0001), and during recovery from hypoglycemia, glyburide inappropriately stimulated insulin secretion, whereas glimepiride did not.[56] In a 14-week study (N=304), patients treated with glimepiride (range 1–8 mg/day vs. placebo) did not report hypoglycemia.[49]

Thiazolidinediones (pioglitazone)

Thiazolidinediones, introduced in 1996, have an attractive mechanism of action with many putative metabolic benefits, but their initial popularity plummeted with concerns over adverse events. Pioglitazone decreases peripheral and liver insulin resistance, resulting in less hepatic glucose output and peripheral insulin resistance.[16] Its benefits of improved lipid profiles and less hypoglycemia compared to sulfonylureas increase its value to those with hyperlipidemia and at risk for low blood glucose.[57]

MAX and EFF.—Pioglitazone is initiated at 15–30 mg, and its MAX is 45 mg/day.[1,16,58] Pioglitazone exhibits a dose response, with an EFF of 45 mg/day (HbA1c: −0.7% to −1.9%), with a greater response in treatment-naïve patients.[16,33] The glycemic effects of pioglitazone improve linearly until at least 26 weeks,[16,58] but longitudinal studies are needed for definitive determination of timeframes. This review focuses on pioglitazone, as rosiglitazone is not a low-cost medication.

Adverse events

Bladder cancer.—Concerns about bladder cancer resulted in the removal of or radical reduction in pioglitazone use in several countries and prompted litigation in the US.[6] However, many of these concerns were found to be unwarranted, and prescribing of pioglitazone resurged.[59] A possible association with bladder cancer was noted in male but not female rats or in either sex for mice, dogs, and monkeys.[59] In one randomized, controlled trial, there appeared to be increased incidence of bladder cancer in the pioglitazone arm the first year of the study, but after 7.8 years, there were more cases in the placebo group (21 vs. 14 cases, respectively).[60] In the most-recent large epidemiologic studies, no associations with bladder cancer have been found.[61,62] However, the early years resulted in international concern, and despite a lack of evidence, a large pharmaceutical company established a $2.4 billion pool to settle lawsuits.[6] Yet the warning for bladder cancer remains active, requiring healthcare professionals to disclose potential risks to avoid liability.[16]

Vascular.—In a meta-analysis of 19 trials (N=16,390), myocardial infarction and stroke prevalence was less in the pioglitazone arm than placebo arm (4.4% vs. 5.7%, RR 0.82, 95% CI 0.72–0.94, p=0.005).[63] Serious heart failure was associated with pioglitazone use but without associated mortality.[63] In addition, pioglitazone has also been shown to reduce negative cardiovascular outcomes among patients with insulin resistance and prediabetes.[64] Furthermore, a recent meta-analysis showed that pioglitazone reduces the risk of recurrent stroke (HR 0.68, 95% CI 0.5–0.92).[65]

Weight gain.—The effect of weight gain includes components of fluid retention in addition to increased adiposity. Although there is an increase in adipose tissue, it is selectively peripheral and not visceral and risks including stroke, cardiovascular disease, and metabolic syndrome are associated with the latter.[66–68] Weight changes have been found to follow a dose response (placebo: −1.4 kg; 15 mg: 0.9 kg; 30 mg: 1.0 kg; 45 mg: 2.6 kg).[16]

Fractures.—Two meta-analyses, which were primarily rosiglitazone trials, suggested a doubled risk of fractures in women, but this was not observed in men.[13,14] A more-recent meta-analysis analyzing only pioglitazone trials found no increase in fractures in patients with type 2 diabetes.[69] A 5-year, non-diabetes clinical trial for secondary stroke prevention found no increased risk of fractures in males or females taking pioglitazone versus placebo (13.6% vs. 8.8%, respectively).[70] Avoiding pioglitazone in high-risk patients, including those with a history of tobacco abuse or low BMI, could promote its potential benefits.

The Table and Figure summarize data regarding low-cost OHMs.

DISCUSSION

Low- and middle-income individuals are significantly and disproportionately affected by diabetes.[2,3,8] This is complicated by the scare options of low-cost therapy available and the controversy of potential adverse events amongst these medications. It is critical to provide sustainable, safe medications to these individuals to reduce sequelae.[9,20] The findings of this study are encouraging; Metformin, glimepiride, and pioglitazone are safe, efficacious, and low-cost options. Further, prescribing the EFF rather than the MAX, such as for glyburide, may reduce or eliminate negative dose-related outcomes including cardiovascular events.[1,41,42]

Since there is limited data comparing low-cost OHMs individually, we compare our findings to other class-based rather than individual drug-based studies. Metformin as a first-line OHM is consistent with current recommendations[1,8,9], but glimepiride and pioglitazone remain controversial second-line therapies due to perceived adverse events.[5,10,50] Sulfonylureas exhibited drug- rather than class-specific adverse events, and the main concern of bladder cancer associated with pioglitazone was not supported by significant evidence.[5,6,55,59–62] Furthermore, adverse events were often dose-related, and patients are frequently prescribed doses greater than those which were effective.[4,41–43] For example, the MAX for glyburide was 20 mg/day, but the EFF was 2.5–5 mg/day, and significant negative cardiovascular outcomes have not been reported at doses ≤10 mg/day.[1,41,42] The statins provide a similar example of wide variation between individual drugs within a class; They have demonstrated dose-related adverse events, and their MAX may be significantly higher than their EFF.[1,71,72] Further research is warranted to evaluate the adverse-event profiles of sulfonylureas at the EFF rather than MAX.

The reported HbA1c effects of OHMs (~1–2%) (Table) may be a function of baseline glycemic control, duration of treatment, and time since diagnosis.[58] For example, studies are typically <30 weeks and include patients with average baseline HbA1c near 8%.[15,16,33] A 52-week study with participant HbA1c levels >11% revealed that OHMs decreased HbA1c levels to 4.6% compared to insulin.[22]

The time to achieve peak HbA1c reduction should also be considered. For instance, peak HbA1c reductions with sulfonylureas were evident by 12–20 weeks, whereas those with metformin and pioglitazone lasted beyond 25 weeks.[16,27,33,44,46,47] These findings suggest that current recommendations assuming full therapeutic effects by 12 weeks are premature.[1,10] A meta-analysis of OHM randomized controlled trials found that <30% of studies lasted beyond 24 weeks.[33] Longitudinal studies are needed to fully determine the time-to-peak HbA1c reduction.

Some investigations have shown value of OHMs beyond and, at times, independent of glycemic control.[73] A meta-analysis of eight RCTs evaluating six OHM combinations with metformin found that almost all (n=5/6) improved cholesterol values and two (exenatide/metformin, vildagliptin/metformin) increased insulin sensitivity.[74] Investigators have stated the need for a paradigm shift in diabetes care from the predominantly glucocentric view of

management to holistic care including sustainable access, individualized glycemic targets, minimizing complications and treatment burdens, and improving quality of life.[73]

Conclusions

This study highlighted several key findings for safe, efficacious, and affordable OHMs: metformin, glimepiride, and pioglitazone. Sulfonylureas and thiazolidinediones should be evaluated as individual drugs and not generalized as a class because their dosing and adverse-event profiles differ. Glimepiride is the preferred sulfonylurea because its adverse event profile differs from others in its class. Awareness of the EFF compared to the MAX is critical to avoid negative dose-related outcomes while optimizing therapy. Further studies are needed to determine OHM protocols for patients in low- and middle-income settings.

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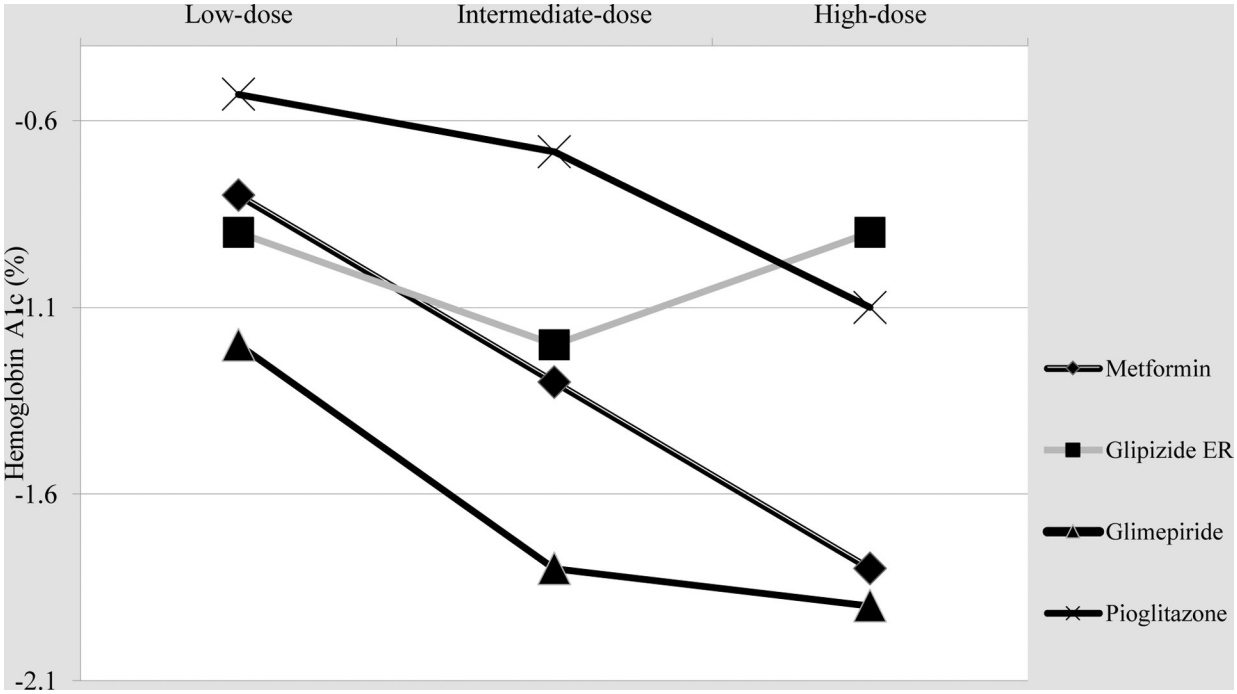

Figure.
Dose-response of low-cost oral hypoglycemic agents.

Table.

Overview of low-cost oral hypoglycemic medications (OHMs)

OHM	Initial dose (mg/day)	MAX[a](mg/day)	EFF[b](mg/day)	Time-to-peak HbA1c effect(week)	Change in HbA1c (%) (range)[c]	Adverse events
Glimepiride	1–2	8	4–8	12–14	−1.0 to −1.9	non-severe hypoglycemia[d]
Glipizide **IR**[e] **ER**[f]						hypoglycemia weight gain
IR[e]	5	40	20	16	−0.9 to −1.8	
ER[f]	5	20	5			
Glyburide/ Glibenclamide	2.5–5	20	2.5–5	12–20	−1.1 to −1.2	Beta-cell loss CVD[g] CI[h]in RI[i] hypoglycemia weight gain
Metformin						B12 deficiency CI in RI stomach upset
IR	500–850	2550	1500–2000	25–39	−0.5 to −2.0	
ER	500-850	2000	1500-2000			
Pioglitazone	15–30	45	45	26	−0.7 to −1.9	weight gain fractures

[a]**MAX:** Maximum recommended daily dose.

[b]**EFF:** Most effective daily dose.

[c]Range of EFF for all studies.

[d]Severe hypoglycemia <50 mg/dL[23].

[e]**IR:** Intermediate release.

[f]**ER:** Extended release.

[g]**CVD:** Cardiovascular disease.

[h]**CI:** Contraindicated.

[i]**RI:** Renal insufficiency.