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PHARMACOLOGIC TREATMENT OF TYPE 2 DIABETES (HE LEBOVITZ AND G BAHTIYAR, SECTION EDITORS)

Adjuvant Pharmacotherapies to Insulin for the Treatment of Type 1 Diabetes

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Abstract

Purpose of Review Insulin therapy alone fails to achieve target glycemic control in the majority of individuals with type 1 diabetes (T1D), motivating the investigation of additive medications. This review focuses on the recent findings on the use of adjunctive pharmacotherapy in T1D.

Recent Findings Metformin and glucagon-like peptide-1 receptor agonists have been associated with weight reduction and decrease in daily insulin requirements without sustainable improvement in glycemic control. Sodium-glucose cotransporter (SGLT)-2 inhibitors, dual SGLT-1/2 inhibitors, and pramlintide have been shown to reduce hemoglobin A1c, induce weight loss, and lower insulin dose. The benefits of dipeptidyl peptidase-4 inhibitors, thiazolidinediones, and alpha glucosidase inhibitors appear to be more limited. Gastrointestinal symptoms and increased hypoglycemia are adverse effects of certain classes.

Summary Although not devoid of side effects, additive pharmacotherapies in T1D can improve glycemic control and lower body weight and insulin requirement. Longer studies are needed before consideration for widespread clinical care.

Keywords Type 1 diabetes · Adjuvant therapy, metformin · GLP-1 receptor agonists · SGLT-2 inhibitors · SGLT-1/2 inhibitors

Introduction

The mainstay of treatment for type 1 diabetes (T1D) has not changed since the first use of exogenous insulin in 1922. The landmark Diabetes Control and Complications Trial in 1993 set the stage for widespread use of intensive insulin management in individuals with T1D to reduce the onset and progression of microvascular complications [1]. The follow-up observational Epidemiology of Diabetes Interventions and Complications Study showed an additional cardiovascular disease benefit with intensive insulin management [2]. The results of these important studies formed the basis of the American Diabetes Association's recommendations for target hemoglobin A1c (HbA1c) of < 7.5% in children and < 7% in adults with T1D [3, 4].

Despite the importance of glycemic control in mitigating the risk of diabetes-associated complications, only approximately 20% of the children and 25% of the adults in the large T1D Exchange Clinic Registry (16,061 participants) achieved target HbA1c [5•]. Part of the difficulty in reaching glycemic target stems from the inability of current insulin therapy to address pathophysiological disturbances in T1D apart from endogenous insulin deficiency including alpha-cell dysfunction [6, 7] and insulin resistance secondary to overweight/obesity [8, 9, 10••]. Thus, additive treatments to insulin may improve glycemic control by targeting different disease processes beyond what is achieved by insulin replacement therapy. This review focuses on adjunctive pharmacotherapy options to insulin in the treatment of T1D.

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Search Strategy and Selection Criteria

We searched the PubMed using the terms "adjuvant therapy," "metformin," "glucagon-like peptide-1 receptor agonists," "GLP-1 receptor agonists," "dipeptidyl peptidase-4 inhibitors," "DPP-4 inhibitors," "SGLT-2 inhibitors," "SGLT-1/2 inhibitors," "amylin receptor agonist," "thiazolidinediones," and "alpha glucosidase inhibitors" combined with the terms "type 1 diabetes" to identify the reference articles published in English during the last 5 years. We also reviewed authors' bibliographies for relevant past studies.

Additive Treatments to Insulin

Metformin

Metformin is the preferred initial medication in individuals with type 2 diabetes (T2D) [3, 11, 12]. It is approved by the Food and Drug Administration (FDA) for treatment of T2D in individuals 10 years of age and older, but not for T1D. Metformin works primarily by decreasing hepatic glucose production, improving peripheral insulin sensitivity, decreasing intestinal glucose absorption, and increasing postprandial glucagon-like-peptide-1 levels [13•]. It generally is well tolerated [12]. Gastrointestinal side effects are common but usually mild. Because of its easy tolerability, affordability, and mechanism of actions, metformin has been of clinical interest as an adjunctive treatment of T1D.

Although earlier randomized controlled trials (RCTs) of shorter durations showed improvement in HbA1c with addition of metformin, more recent and larger RCTs failed to show this benefit. In a meta-analysis of four RCTs and a prospective controlled study with durations of 3–6 months ($n = 149$) in adults and children, Pang et al. found a small but statistically significant reduction in levels of HbA1c (~ 0.3%) and a moderate reduction in total daily insulin dose without significant increase in adverse events or change in weight [14]. A systematic review of five RCTs with combined effects estimated by Vella et al. showed that metformin was associated with decreased daily insulin dose (6.6 units/day, $p < 0.001$) and weight reduction in some studies but no significant HbA1c reduction (~ 0.1%, $p = 0.42$) [15]. Metformin was well tolerated, with minimal gastrointestinal side effects, but there was a trend towards development of hypoglycemia. Codner et al. evaluated the effect of metformin on 24 adolescent girls with T1D and hyperandrogenism in a RCT for 9 months [16]. Assessment of secondary outcomes revealed no difference in levels of HbA1c or daily insulin doses. Two other RCTs that included adolescents with T1D failed to show statistically significant reduction in levels of HbA1c, although a decrease of 0.4% in the level of HbA1c occurred at 6–9 months [17, 18]. However, Nadeau et al. found significant reduction in insulin dose, BMI z-score, and waist circumference with low-dose metformin (500 mg twice a day) at 6 months compared to baseline (within group comparison) in adolescents, but these findings were not significantly different from those individuals given a placebo. An analysis from the German/Austrian Diabetes Patienten Verlaufsdokumentation (DPV) registry in Germany and Austria that evaluated the effects of metformin in addition to insulin in pediatric individuals with T1D showed a slight reduction of BMI standard deviation score (BMI-SDS) but no improvement in HbA1c or insulin requirement during an average treatment period of 1.4 years [19•]. A multicenter RCT conducted by Libman et al. involving 140 adolescents in T1D Exchange Clinic Registry revealed no difference in HbA1c at 26-week follow-up with metformin compared to the placebo group [20•]. However, a higher percentage of participants in the metformin group had ≥ 25% reduction in total daily insulin/kg of body weight (23% vs 1% in placebo group) and ≥ 10% reduction in BMI z-score (24% vs 7% in placebo group). Not surprisingly, there were more participants with gastrointestinal side effects in the metformin group than in the placebo group. Liu et al. reported similar findings in a meta-analysis including eight RCTs with 300 participants [21]. There were reductions in weight, total daily insulin dose, and total and low density lipoprotein (LDL) cholesterol but no effect on HbA1c or fasting plasma glucose with metformin use. Although an increase in gastrointestinal side effects occurred, metformin did not increase the risk of severe hypoglycemia. A systematic review and meta-analysis of six RCTs with 325 children with T1D showed consistent results, with decreased total daily insulin dose, BMI and BMI z-score, but similar levels of HbA1c [22•]. In contrast to these findings, in a 10-year retrospective study, Staels et al. showed that adjuvant metformin added to intensive insulin therapy in individuals with T1D had no long-term beneficial effects on BMI, HbA1c, or insulin dose, although small but non-significant decreases were seen in BMI and insulin dose in the first years of metformin therapy [23]. The REMOVAL trial, the largest and longest RCT of metformin in T1D for 3-years duration, studied 428 adults with T1D older than 40 years with at least 5 years of diabetes and at least 3 of 10 cardiovascular risk factors [24••]. The addition of metformin did not significantly change glycemic control or mean carotid artery intima media thickness, a surrogate of atherosclerosis progression. However, metformin use was associated with reductions in body weight, LDL cholesterol, and insulin dose requirement. Although gastrointestinal adverse effects and vitamin B_{12} deficiency were increased in prevalence in the metformin group, risk of hypoglycemia did not change. Most recently, in a meta-analysis of 13 RCTs with 1183 individuals with T1D, Meng et al. found reductions in BMI, insulin requirements, total cholesterol, and LDL cholesterol but not in levels of HbA1c with use of metformin. Additionally, metformin was associated with a slight increase in risk of severe

hypoglycemia and gastrointestinal side effects [25]. Findings from recent RCT are summarized in Table 1.

Overall, available data do not show evidence of sustainable improvement in glycemic control with use of adjunctive metformin in individuals with T1D. However, metformin appears to have other benefits including weight reduction, improvement in lipid profile, and decrease in total daily insulin requirement which may translate to decreased risk of developing cardiovascular disease. Gastrointestinal adverse effects have been reported consistently, whereas metformin does not appear to increase the risk of hypoglycemia.

GLP-1 Receptor Agonists and DPP-4 Inhibitors

Glucagon-like peptide-1 (GLP-1) is an incretin produced by intestinal cells in response to a meal stimulus [26]. It stimulates insulin secretion in a glucose-dependent manner, inhibits secretion of glucagon, slows gastric emptying, and reduces food intake by inducing satiety [27]. Additionally, it improves proliferation/survival of beta cells, peripheral insulin sensitivity, and cardiac output, and decreases hepatic glucose production [28]. After its secretion, GLP-1 is rapidly (in minutes) degraded by dipeptidyl peptidase-4 (DPP-4). Two classes of pharmacological agents target this incretin-mediated physiological process. Whereas GLP-1 receptor agonists are resistant to degradation by DPP-4, DPP-4 inhibitors enhance the action of endogenous incretins by inhibiting their degradation. Although GLP-1 receptor agonists may cause gastrointestinal side effects, DPP-4 inhibitors usually are well tolerated. Currently, six GLP-1 receptor agonists (i.e., exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide, and semaglutide) and four DPP-4 inhibitors (i.e., sitagliptin, saxagliptin, linagliptin, and alogliptin) are approved by the FDA for treatment of T2D but not T1D [12, 29].

Wang et al. examined seven RCTs on the effects of additive GLP-1 receptor agonists in T1D through a systematic review and meta-analysis [30•]. A total of 206 adults were included in the analysis with study durations from 12 weeks to 15 months. They found that adjunctive GLP-1 receptor agonists were associated with a statistically significant but small reduction in levels of HbA1c (0.2%), decrease in body weight, and weight-adjusted-bolus insulin doses. An in-depth review of individual studies shows that use of GLP-1 receptor agonists resulted in generally 0–0.2% statistically non-significant difference in HbA1c reduction, approximately 3.0–6.8-kg weight loss, and 5–8-units decrease in total daily insulin dose, driven mainly by the decrease in bolus insulin requirement with GLP-1 receptor agonist use. Its use was associated with increased gastrointestinal side effects consistently but not with hypoglycemia [31–33, 34•].

Another recent systematic review and meta-analysis studied the effects of DPP-4 inhibitors in the treatment of T1D in adults and youth [35•]. Five RCTs were eligible for analysis ($n = 253$). Overall, DPP-4 inhibitors did not significantly affect HbA1c, weight, daily insulin requirement, or incidence of hypoglycemia. However, they were associated with reduced levels of glucagon during hyperglycemia [36], improved beta-cell function [37], and post-meal rise in levels of endogenous GLP-1 [38] in individual studies. In contrast, Guo et al. found in a meta-analysis of six RCTs that DPP-4 inhibitors decreased daily insulin requirements significantly (2.4 units/day) without any significant change in HbA1c or incidence of hypoglycemia [39•]. Lastly, both human and rat studies suggest that DPP-4 inhibitors may be beneficial for diabetic nephropathy [40, 41]. On the other side, there are concerns for association between DPP-4 inhibitor use and pancreatic and thyroid cancer [42]. However, in a recent systematic review and meta-analysis assessing 12 RCTs and 13 observational studies, Overbeek et al. reported that there was no statistically significant risk for pancreatic or thyroid cancer [43].

Overall, neither adjunctive GLP-1 receptor agonists nor DPP-4 inhibitors provide any substantial benefit for glycemic control in individuals with T1D. However, GLP-1 receptor agonists were associated consistently with weight loss and decreased daily insulin requirements at an expense of increased gastrointestinal side effects. The benefits of DPP-4 inhibitors in individuals with T1D appear to be more limited based on available data.

SGLT-2 and SGLT-1/2 Inhibitors

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors work primarily by increasing excretion of glucose in the urine secondary to blocking reabsorption of glucose in the proximal renal tubule [44]. In comparison, dual SGLT-1/2 inhibitor additionally blocks SGLT-1, a major transporter of glucose in the intestines, and decreases intestinal reabsorption of glucose as well [45]. Three SGLT-2 inhibitors (i.e., canagliflozin, dapagliflozin, and empagliflozin) are FDA-approved for the treatment of T2D but not for T1D. The dual SGLT-1/2 inhibitor sotagliflozin is still an investigational drug, for which the FDA has just recently accepted its marketing application for review as an adjunct therapy in T1D [46]. The FDA issued a warning with regard to euglycemic diabetic ketoacidosis with SGLT-2 inhibitors in individuals with T1D and T2D, based on reported cases [47•].

We identified three RCTs assessing adjunct SGLT-2 inhibitors in T1D with study durations of 2–18 weeks. In a 4-week RCT involving 75 individuals, Pieber et al. found that additive empagliflozin was associated with 0.5% reduction in levels of HbA1c and 1.9-kg weight loss without increased risk of symptomatic hypoglycemia [48•]. Further analysis also showed decreased glycemic variability and increased time spent in target glycemic range without increasing time spent in hypoglycemia [49•]. Similarly, in a RCT involving 351 participants who were followed for 18 weeks, Henry et al.

Table 1 Summary of randomized controlled trials published in the last 5 years assessing metformin as an adjunctive treatment to insulin in T1D

Reference	Dose (daily)	Patient characteristics (selected)	*N*	Study duration	Pertinent results	Adverse effects
Codner et al. [16]	850 mg BID	Adolescents with T1D and hyperandrogenism	24	9 months	No significant change in HbA1c No significant change in daily insulin doses	Mild gastrointestinal symptoms and mild headaches
Nadeau et al. [17]	500 mg BID	Pubertal adolescents with T1D	74	6 months	No significant change in HbA1c (metformin vs placebo)	No reported severe hypoglycemia, diabetic ketoacidosis, or other severe adverse effects
					No significant change in total daily insulin dose. (However, the changes were significant in both groups upon to baseline, $p < 0.05$ within-group comparison)	No difference between groups in gastrointestinal symptoms or ketones
					No significant change in BMI *z*-score. (However, the changes were significant in metformin group upon to baseline, $p < 0.05$ within-group comparison)	
					Decreased waist circumference at 3 and 6 months	
Nwosu et al. [18]	1000 mg	Adolescents with T1D and BMI > 85th percentile	28	12 months	No significant change in HbA1c (metformin vs placebo)	No difference in mild hypoglycemia episodes
					No significant change in total daily dose of short-acting or long-acting insulin per kilogram body weight	One instance of severe hypoglycemia requiring third party assistance in a subject in metformin group following reduced caloric intake but none in placebo group
Libman et al. [20]	1000 mg BID	Adolescents with T1D, BMI ≥ 85th percentile, and total daily insulin dose ≥ 0.8 u/kg/day	140	26 weeks	Glycemic control, Baseline HbA1c 8.8% in each group At 13 weeks, significantly greater reduction in HbA1c in metformin group (− 0.2 vs 0.1%, mean difference $p = 0.02$, 0.3%) At 26 weeks, no difference in change in HbA1c from baseline (0.2% reduction in each group) Total daily insulin dose, At 26 weeks, was reduced by ≥ 25% from baseline among 23% of metformin group vs 1% of placebo group (mean difference 21%)	More gastrointestinal symptoms in metformin group
					BMI *z*-score, At 26 weeks, ≥ 10% reduction in BMI *z*-score from baseline among 24% of metformin group vs 7% placebo group (mean difference 17%)	
Petrie et al. [24]	1000 mg BID	Adults ≥ 40 years old with T1D ≥ 5 years and have ≥ 3 out of 10 specific cardiovascular risk factors	428	3 years	Statistically significant but clinically insignificant reduction in HbA1c (metformin vs placebo), Baseline, 8.08% vs 8.02%	Gastrointestinal side effects and vitamin B_{12} deficiency were more common in metformin group
					At 36 months, 8.1% vs 8.1% (0.13% reduction with metformin, $p = 0.006$) No reduction in insulin dose requirement with an average over 3 years. However, there was little difference between treatment groups in the first 6 months, followed by a small but sustained reduction in participants treated with metformin (− 0.023 u/kg, $p = 0.045$)	No difference in hypoglycemia (per patient-year)
					Reduction in body weight with metformin compared to placebo (1.17 kg)	
					Reduction in LDL cholesterol with metformin compared to placebo (0.13 mmol/L)	

reported that with adjunct canagliflozin, compared to placebo group, there were ≥ 0.4% reduction in HbA1c in 41% of individuals, average weight loss of 4.4 kg, and decrease in total daily insulin requirement by 7.6 units but increased incidence of ketone-related adverse events (9.4% vs 0% in placebo group) including diabetic ketoacidosis (DKA; 6% vs 0% in placebo group). No difference in incidence of hypoglycemia was noted among the groups [50•]. It also improved time spent in target glycemic range and reduced time spent in hyperglycemia [51]. In a 2-week pilot RCT with dapagliflozin, Henry et al. found a reduction in average daily glucose level by 41 mg/dL and total daily insulin dose by 16% without any incident of DKA [52]. Furthermore, empagliflozin may preserve beta-cell mass in a rat model of T1D [53•].

The dual SGLT-1/2 inhibitor sotagliflozin is emerging as a potential adjunct treatment in T1D. In a RCT involving 33 participants with a treatment duration of 1 month, Sands et al. showed that dual SGLT-1/2 inhibition decreased bolus insulin dose by 32% and total daily insulin dose by 15%, reduced levels of HbA1c by 0.5%, decreased body weight (1.7 kg), and increased time in target glycemic range by 11% [54•]. The participants had increased incidence of gastrointestinal symptoms with SGLT-1/2 inhibitor compared with placebo (50% vs 18%). There were two incidents of DKA in the SGLT-1/2 inhibitor group, although both were attributed to pump-related issues. Consistent with these findings, in a multicenter, double-blind, phase 3 study over 24 weeks with 1402 participants with T1D, Garg et al. found that the SGLT-1/2 inhibitor arm compared to controls had reductions of HbA1c (~ 0.5%), weight (~ 3 kg), and daily dose of insulin (~ 5 units/day) but the rate of diabetic ketoacidosis was higher (3% vs 0.6% in placebo) [55•]. Furthermore, a significantly larger percentage of participants achieved HbA1c < 7% without severe hypoglycemia or DKA in SGLT-1/2 inhibitors than placebo (28.6% vs 15.3%).

In summary, SGLT-2 and dual SGLT-1/2 inhibitors are potential adjunctive therapies to insulin in individuals with T1D. While there is a paucity of studies, available data show benefit in HbA1c, weight loss, and reduction in insulin dose although increased incidence of ketone-related adverse events including DKA.

Amylin Receptor Agonists

Amylin is a neuroendocrine hormone co-secreted with insulin from pancreatic beta cells [56]. It stimulates the satiety center, decreases secretion of glucagon postprandially, and delays gastric emptying. Thus, it reduces postprandial glucose excursions. Pramlintide, an amylin receptor agonist, is the only non-insulin agent approved by the FDA as an adjunct therapy to insulin in T1D. It requires injections three times per day, which may add to the burden of T1D management.

The effects of pramlintide as an adjunct therapy in T1D were studied in three main RCTs with durations of 29–52 weeks. In a RCT with 480 participants for 52 weeks, Whitehouse et al. found that reduction of levels of HbA1c was significantly greater in individuals taking pramlintide than in the placebo group throughout the study (0.5%, 0.4%, and 0.3% difference at 13, 26, and 52 weeks, respectively) [57]. At the end of the study, the pramlintide group had a smaller increase in total daily insulin dose (2.3% vs 10.3%), and weight loss (0.5-kg weight loss vs 1-kg weight gain in placebo). Although there was no difference in the rate of severe hypoglycemia events, the rate of adverse events, primarily nausea, was higher in the pramlintide group (47% vs 22%). In a multicenter RCT, Ratner et al. showed that pramlintide was associated with significant reductions in levels of HbA1c (~ 0.3%) and body weight (0.4-kg loss vs 0.8-kg gain in placebo) over 52 weeks. Mild-to-moderate nausea was the most common adverse event with pramlintide [58]. In contrast to these two RCTs, Edelman et al. showed no difference in HbA1c between the pramlintide and placebo groups at 29 weeks [59]. However, pramlintide significantly decreased postprandial glucose excursions, weight (1.3-kg weight loss vs 1.2-kg weight gain), and insulin dose (reduction by 28% vs 4%). There were higher incidence of nausea, severe hypoglycemia, and decreased appetite in the pramlintide group compared to the placebo group. The authors postulated that lack of a difference in HbA1c was anticipated because of the study design, in which insulin doses were adjusted for pre-specified glycemic targets in both groups.

Overall, pramlintide may be beneficial in glycemic control, weight loss, and reduction of insulin doses, but it comes with an increased risk of gastrointestinal side effects and hypoglycemia.

Thiazolidinediones

Thiazolidinediones are peroxisome proliferator-activated receptor-γ agonists that improve insulin sensitivity mainly in peripheral tissues and reduce lipolysis [60]. Pioglitazone and rosiglitazone are the only current FDA-approved thiazolidinediones for treatment of adults with T2D but not in T1D [61]. There are FDA warnings for possible exacerbation of congestive heart failure, myocardial infarction, bladder cancer, fatal hepatic failure, and higher risk of developing hypoglycemia, fractures (in females), fluid retention, edema, weight gain, and anemia [61].

In four RCTs assessing the efficacy of pioglitazone or rosiglitazone in individuals with T1D, there were 0–0.2% reduction in placebo-adjusted HbA1c and mixed results in other parameters [62–65]. Whereas Strowig et al. and Stone et al. reported decreased insulin requirements compared to placebo; no difference was found between the groups in the studies conducted by Zdravkovic et al. and Bhat et al. Increased

BMI was reported in only one of these studies [64]. Neither rosiglitazone nor pioglitazone was found to be associated with increased risk of hypoglycemia.

Overall, the potential benefits of thiazolidinediones do not seem to justify the possible risks associated with them in individuals with T1D.

Alpha Glucosidase Inhibitors

Alpha glucosidase, an enzyme in the proximal small intestine, plays an important role in carbohydrate absorption due to its role in breaking down disaccharides and more complex carbohydrates [60]. Alpha glucosidase inhibitors delay intestinal absorption of carbohydrates and reduce postprandial glucose excursions by inhibiting this enzyme. Acarbose and miglitol are the available FDA-approved alpha glucosidase inhibitors in the treatment of adults with T2D but not in those with T1D [61]. The main side effects are flatulence and diarrhea.

There are no recent RCTs assessing alpha glucosidase inhibitors in T1D. In older studies, Hollander et al. reported that additive treatment with acarbose was associated with reduction in mean postprandial glucose levels by 59 mg/dL and HbA1c by 0.48% in participants with T1D in a 36-week multicenter RCT [66]. In contrast, Riccardi et al. showed that acarbose had no significant effect on HbA1c but reduced 2-h postprandial glucose levels in a 24-week multicenter RCT [67]. Gastrointestinal side effects were more common with acarbose, but it was not associated with hypoglycemia in both of these studies. In a 12-week, open-label study of participants with T1D receiving intensive insulin therapy, Nagai et al. showed a significant reduction in levels of HbA1c (0.5%), postprandial glucose, BMI, and daily bolus insulin dose but increase in postprandial GLP-1 levels [68].

Overall, alpha glucosidase inhibitors decrease postprandial glucose levels with potentially small HbA1c benefit without increased risk of hypoglycemia in individuals with T1D. Gastrointestinal side effects may limit its use.

Conclusions

Although only one agent (i.e., pramlintide) is currently approved by the FDA as an additive treatment in individuals with T1D, other agents used in T2D have potential benefits in individuals with T1D for glycemic and non-glycemic therapeutic goals.

Metformin has not been shown to provide sustainable improvement in glycemic control, but it has been shown to be helpful with weight reduction, improvement in lipid profiles, and decrease in insulin requirements with potential cardiovascular benefits. Studies to date have not shown any significant glycemic benefit of GLP-1 receptor agonist and DPP-4 inhibitors in individuals with T1D. However, GLP-1 receptor agonists have been associated with weight loss and decreased daily insulin requirement, but also with gastrointestinal side effects. The benefits of DPP-4 inhibitors appear to be more limited compared to GLP-1 receptor agonists. Both SGLT-2 and dual SGLT-1/2 inhibitors are promising adjunctive therapies to insulin in individuals with T1D, despite the paucity of studies. Available data showed reduction in HbA1c, weight, and insulin dose. However, the increased incidence of ketone-related adverse effects, including diabetic ketoacidosis, is an important limitation for its use. Similarly, pramlintide may be beneficial for glycemic control, weight loss, and reduction of insulin doses, but it has an increased risk of gastrointestinal side effects and hypoglycemia. The potential benefits of thiazolidinediones do not seem to justify the possible risks associated with them in individuals with T1D. Alpha glucosidase inhibitors decrease postprandial glucose levels with potential HbA1c benefit without increased risk of hypoglycemia in individuals with T1D.

In conclusion, clinicians considering an additive pharmacologic agent to insulin in their patients with T1D should consider FDA approval status and assess individualized risk-benefit ratios. Further studies with longer follow-up durations are needed before recommending their widespread use in clinical practice.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human participants or animals performed by any of the authors.

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- • Of importance
- •• Of major importance

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