Published in final edited form as:

Expert Rev Clin Pharmacol. 2019 May ; 12(5): 471–479. doi:10.1080/17512433.2019.1597705.

Pharmacologic Treatment Options for Type 1 Diabetes: What's New?

Laura M. Nally¹, Jennifer L. Sherr¹, Michelle A. Van Name¹, Anisha D. Patel¹, and William V. Tamborlane¹

¹Yale Children's Diabetes Program, Yale University School of Medicine, New Haven, CT, USA

Abstract

Introduction: The expanding variety of insulins, including biosynthetic human insulin and rapid and long-acting insulin analogs, have dramatically transformed the management of type 1 diabetes (T1D) over the past 25 years. Moreover, increasing interest in the use of novel drugs developed for the treatment of type 2 diabetes (T2D) as adjunctive therapies for T1D remains a work in progress.

Areas Covered: We reviewed articles published up to December 2018 in PubMed and [ClinicalTrials.gov](https://clinicaltrials.gov) for recent developments in the pharmacologic treatment of T1D, including inhaled insulin, ultrafast and ultralong-acting insulins and adjunctive therapies including pramlintide, metformin, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2, and SGLT1/2 inhibitors.

Expert Opinion: With the creation of ultrafast-acting insulin analogs and very prolonged duration of action of basal insulins, it is possible to more closely mimic physiologic insulin secretion. Adjunctive therapies, likewise, may also overcome some of the abnormal physiology that is a hallmark of T1D. Therefore, individualized consideration of the efficacy of these agents must be measured alongside the potential adverse effects when choosing an adjunctive therapy.

Keywords

type 1 diabetes; insulin; analogue; adjunctive therapy; inhaled insulin; ultrafast insulin; GLP-1 receptor agonists; SGLT-2; pramlintide

1. Introduction

For more than 50 years, regular, NPH and Lente insulins derived from the pancreata of animals were the only insulins available for treatment of type 1 diabetes (T1D). Not only were the impurities in these preparations prone to immunologic complications, but the standard of care was to give one or two subcutaneous injections per day. Treatment of T1D was transformed in the late 1970's and early 1980's by development of the first blood

Corresponding Author: Laura M. Nally, laura.nally@yale.edu, phone 203-785-5809, fax 203-737-7635.

Declaration of Interest

WV Tamborlane is a consultant for Boehringer Ingelheim, Eli Lilly, Medtronic Diabetes, Novo Nordisk and has received grants support from AstraZeneca, Boehringer Ingelheim and Takeda. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

glucose meters, introduction of glycosylated hemoglobin assays (A1c), use of recombinant gene technology for the production of regular human insulin, and demonstration of the effectiveness of basal/bolus therapy using portable continuous subcutaneous insulin infusion (CSII) pumps.

As laboratory methods advanced, scientists were able to modify the chemical structure of insulin to allow it to be absorbed more rapidly [1]. In contrast to regular human insulin, with a duration of action up to 7–8 hours, the more rapid absorption of lispro, aspart and glulisine insulins were better able to mitigate early post-meal peaks in plasma glucose and decrease the risk of late post-prandial hypoglycemia [2]. Moreover, the lower peaks and longer-duration of action of new long-acting basal insulin analogs like glargine and detemir provided a better means to regulate overnight and between meal glucose control.

Additionally, exclusive use of rapid-acting insulin analogs in insulin pump therapy allowed clinicians and patients to tailor insulin doses more precisely. In head-to-head comparisons, CSII was able to surpass multiple daily injections (MDI) treatment for T1D over glargine and isophane insulin types [3–5].

While the first generation of rapid and long-acting insulin analogs represent great advances over prior insulin preparations, there is still room for improvement. Specifically, the peak action of bolus doses of rapid-acting insulin analogs is usually ~120 min after dosing and the duration of action exceeds 5 hours [6]. Conversely, the duration of action of long-acting analogs is 24 hours and there is considerable intra-subject day to day variation[7]. More recently, new drugs in different classes have been approved to treat Type 2 diabetes (T2D) and many others are being developed [8]. In this report, we will review the latest developments in the pharmacology of using T2D drugs to treat T1D.

In this review, we searched PubMed and [ClinicalTrials.gov](https://clinicaltrials.gov) for articles that pertained to new insulin types that had been developed in the last 5–7 years and presented clinical trial data on each of these. We also reviewed the FDA published data on each of the insulin types and approval dates. Further, clinical trials evaluating the safety, efficacy, and clinical utility of each of these newer insulin types and insulin analogues will be reviewed here.

2. NEW ULTRAFAST AND ULTRALONG-ACTING INSULINS

2.1 Ultrafast-Acting Insulin Analogues

Insulin molecules in aqueous solutions tend to self-aggregate, with hexamers being the most abundant form in insulin vials and pens. However, in order to be absorbed into the circulation, hexamers need to dissociate into dimers or monomers, which is a relatively slow process with regular human insulin. The first generation of rapid-acting insulin analogs still self-aggregate in aqueous solution. However, hexamers of insulin analogs with amino-acid substitutions in the β -chain dissociate more rapidly than regular human insulin once injected under the skin. Importantly, these biosynthetic modifications do not adversely affect the glucose-lowering actions of these analogs. A focus of more recent pharmacological research has been on additional modifications to increase the rate of absorption of rapid-acting insulin analogs even further (i.e., ultrafast-acting insulin analogs).

Fast-acting insulin aspart (Fiasp) Insulin is the first insulin of its class and was approved by the FDA in September 2017. More rapid absorption and action of aspart insulin is achieved by altering the excipients in the aqueous solution: L-arginine for stabilization of the insulin molecule in solution and niacinamide for more rapid absorption [9]. In a pooled analysis, Fast-acting insulin aspart appeared earlier in the circulation by ~5 minutes and began to lower glucose ~15 minutes sooner [10]. In a 52 week phase III randomized double-blind trial comparing Fiasp to conventional aspart (IAsp), Fiasp treatment led to a slight decrease in A1c [11]. Additionally, 1-hour postprandial glucose values were on average 18 mg/dL lower in those who received Fiasp [11]. In a randomized, double-blind, crossover trial, elderly (≥ 65 years) and young (18–35 years) adults with T1D underwent euglycemic clamp studies to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) effects of Fiasp vs IAsp. The onset of action of Fiasp was 9–10 minutes faster and the glucose lowering effect was greater than IAsp in both age groups [12]. Another randomized double-blind crossover trial that compared Fiasp and IAsp showed a 12% greater suppression of endogenous glucose production and 24% increase in glucose disappearance during the first hour [13]. These findings indicate a modest, incremental improvement in the PD action of Fiasp over IAsp.

Ultrafast-acting insulin lispro (URLi) is currently in development. URLi is formulated with 2 new excipients. Preliminary results of a randomized, double-blind, phase 1b study comparing the PK and PD profiles of URLi and lispro demonstrated that URLi given 15 minutes before eating, at the start of the meal, and 15 minutes after the start of the meal all reduced glycemic excursions at 2 and 5 hours compared to lispro [14]. URLi is currently undergoing phase 3 clinical trials [NCT03465878].

A clinical advantage of ultrafast-acting analogs relates to the timing of pre-meal bolus doses. In a phase 3 study of Fiasp, it was shown that injections of ultrafast-acting analog 20 minutes after starting to eat provides the same meal coverage as an identical dose of aspart injected just prior to eating. We anticipate that this more rapid onset of action will allow for improved quality of life in patients who take their meal boluses after eating, a key management strategy in infants and toddlers with T1D whose carbohydrate intake with meals is unpredictable.

2.2 Insulin Human Inhalation Powder

Alternative routes of insulin administration that obviate the need for insulin injections, such as intranasal, oral and rectal insulin preparations, have been abject failures until recently. Insulin inhalation (Exubera) was the first inhaled insulin preparation that was approved by the FDA in 2006 [15]. Since the bioavailability of this insulin was only ~8–10%, it was supplied in blister packs in 1 mg and 3 mg doses. The inhalable powder was made up of sodium citrate, mannitol, glycine, sodium hydroxide, and regular human insulin. The inhaler was a bong-like tube that allowed for the drug to be inhaled as a cloud of aerosolized powder [15]. Insulin inhalation use was not widely accepted for many reasons, including the need for regular pulmonary function testing due to modest reductions in pulmonary function, a slightly increased incidence of lung cancer that may have been drug-related, and side effects of mild cough and dyspnea [15–19]. This insulin was removed from the market in 2007 after

failed sales [17]. Limitations in the ability to deliver precise doses of inhaled insulin and the more widespread use of insulin pens and insulin pumps in T1D also played roles in the failure of insulin inhalation.

Inhaled insulin was resurrected in 2014 with FDA approval of insulin human inhalation powder (Afrezza) for adults with T1D and T2D [20]. Insulin human inhalation powder (IHIP) comes as an inhaled powder dispensed in cartridges comparable to 4, 8, and 12 units of subcutaneous insulin [19]. The faster onset and more rapid elimination of (IHIP) more closely mimics the cephalic phase of insulin release in response to a meal [19]. The faster on, faster off PK can minimize glycemic excursions from carbohydrate ingestion and prevent insulin stacking that can be seen with subcutaneous injections of rapid-acting insulins.

IHIP uses a drug delivery system that has been studied with PTH, GLP-1 and antiepileptic drugs [19, 21–23]. IHIP is composed of an inert, organic excipient, fumaryl diketopiperazine (FDKP), that auto-encapsulates, stabilizes, and transports peptides by microspheres (diameter ~2 μ m) across the surface of the alveoli into the circulation [19]. The enormous surface area of highly perfused lungs facilitates rapid absorption and avoids first-pass hepatic metabolism, key advantages of inhaled administration. The IHIP system uses an inhaler that only requires 1 inhalation per cartridge [24]. However, patients still require an injection of long-acting insulin for overnight and between meal glucose control. IHIP use is limited to those without asthma, COPD, and chronic lung disease, and should be used in caution with those who smoke. For anyone using this medication, pulmonary function tests must also be performed before initiating, after 6 months of therapy, and then on a yearly basis [19].

An open-label, 24-week noninferiority trial compared the impact of prandial IHIP and subcutaneous aspart on A1c change in 518 adults with T1D. The mean change in A1c from baseline was similar between the groups (–0.19%, 95% CI –0.02 to –0.36) [24]. However, safety assessments were mixed: participants using IHIP had greater weight loss and fewer hypoglycemic events, but the IHIP group also had a small decrease in FEV1 (40ml) that improved after IHIP was stopped[24]. Nevertheless, it remains to be seen whether this iteration of inhaled insulin will be more successful than the first generation of insulin inhalation. Since limited dosing increments may also be a barrier to increased penetrance of IHIP into the care plan for patients with T1D, patients with T2D who require basal/bolus therapy with insulin may be a more appropriate target population.

2.3 Ultralong-acting Insulin Analogs

Glargine was the first once-daily, long-acting insulin analog approved by the FDA in 2000 [25]. The prolonged duration of action of glargine was achieved by amino-acid substitutions that shift the molecule's isoelectric point; making this insulin analog soluble in the weak acid solution in which it is packaged. However, glargine in solution precipitates into crystals when injected into the neutral pH of the interstitial fluid. Consequently, in order for the glargine molecules to separate into hexamers, dimers and monomers after injection, the crystal structure must first dissolve, which is a prolonged process that can stretch over 18–26 hours.

Detemir was the second long-acting analog that was approved by FDA in 2005 [26]. Glucose clamp studies demonstrated that detemir had less intra-subject variability than glargine but other studies suggested that the duration of action of glargine was greater than that of detemir [7]. Consequently, the stage was set for the introduction of new ultralong-acting analogs.

Glargine U300 is a concentrated version of glargine insulin that was FDA approved in 2015 [27]. Clamp studies demonstrated that the duration of action of glargine U300 was considerably longer than glargine U100. A randomized, double-blind, crossover study of glargine U100 compared to glargine U300 in 30 adults who took a steady dose for 8 days and then were evaluated using a 36-hour euglycemic clamp demonstrated the differences between the preparations [28]. The PK and PD profiles were less variable with glargine U300 than glargine U100 [29]. Equally important, steady glucose control was maintained for 5 hours longer with Glargine U300, making the duration of action of glargine U300 consistently 24 hours [28]. Interestingly, in a randomized crossover study of individualized glargine U100 and U300 doses at steady state, endogenous glucose production was increasingly suppressed after the dose of glargine U300 was given, with the least suppression occurring in the first 6 hours, and most suppression 18–24 hours after the dose [29].

Degludec Insulin was approved by the FDA in 2015 for both T1D and T2D at least 1 year of age [30]. The molecular structure of degludec is similar to insulin; however, degludec has a deletion of threonine at B30 and an additional large fatty acid attached to lysine at the B29 position to allow it to form dihexamers in solution [31]. After it is injected into a physiologically neutral pH environment, it creates large strings of hexamers allowing for slow release of insulin monomers, leading to a much longer duration of action [32]. After achieving steady state concentrations, degludec's duration of action lasts up to 42 hours but the glucose lowering effect is minimal after 36 hours. Additionally, up to 160 units of degludec can be given at a single time using the U200 concentration. A randomized, double-blind, crossover trial, involving elderly subjects and young adults with T1D showed that the PK and PD of insulin degludec were similar in both age groups [33]. While studies have shown that there is no difference in the PK between U100 and U200 degludec at the same dose administered, the pharmacokinetic properties of acylated insulins should be interpreted cautiously, as only total insulin levels, rather than free active insulin levels can be measured [34]. Because the insulin solution for degludec is maintained at a pH of 7.6, it may cause less stinging with injections when compared to insulins with a lower pH. Novel features include of both glargine 300 and degludec include FDA approval to be taken any time during the day, rather than at the same time each day, allowing for greater flexibility with timing of insulin dosing.

With the longer duration of action of degludec, it is possible that those with frequent episodes of ketosis and diabetic ketoacidosis due to missed doses of basal insulin could benefit from using this type of insulin, and studies in pediatrics are currently ongoing [NCT03400501].

3. ADJUNCTIVE THERAPIES FOR T1D

It can be argued that little has changed in the treatment of T1D since insulin was introduced in the 1920s. Yes, we have many new insulin preparations, much better ways to monitor the effectiveness of insulin with current blood glucose meters and new continuous glucose monitors, and improved ways to deliver insulin with insulin pumps and now semi-automatic hybrid closed-loop insulin delivery systems. However, the basic pharmacology has not changed: it has always been all about insulin. That is why many clinicians who care for patients with T1D are excited about the possibilities of using the plethora of anti-diabetic drugs that have been approved for use in T2D, as adjunctive agents to insulin in the treatment of T1D.

3.1 Pramlintide (Analogue of Amylin)

Amylin is co-secreted with insulin by beta cells in response to blood sugar elevations. When amylin is secreted, it slows gastric emptying, inhibits glucagon release from the adjacent alpha cells in the pancreatic islet, and promotes centrally-mediated satiety³⁵. Pramlintide (a biosynthetic analog of Amylin) is the only adjunctive therapy that has been FDA approved for use in T1D based on the results of pivotal, randomized phase III studies. Studies showed that pramlintide was efficacious in lowering A1c by ~0.5%. Furthermore, its use is associated with weight loss in overweight or obese patients [36,37]. Pramlintide's putative mechanisms of action in T1D are similar to amylin; it slows gastric emptying and suppresses meal-stimulated increases in plasma glucagon, which combine to mitigate post-prandial hyperglycemia. We have shown that these actions of pramlintide persist over time; whereas, similar actions by liraglutide wane very quickly [38–40]. Even though it was approved by the FDA in 2005, very few patients with T1D are currently being treated with pramlintide. The major obstacle to widespread use of this agent is that it requires an additional 3–4 subcutaneous injections per day, which has proven too cumbersome for the vast majority of patients. More recently exploration of whether a co-formulation of insulin and pramlintide could be used in CSII therapy has been explored and may allow greater penetrance of this agent into clinical practice⁴¹. Additional studies looking at the combination of insulin, pramlintide, and glucagon administered subcutaneously via 3 separate pumps and controlled by a computer-generated algorithm may be able to remove the need for carbohydrate counting altogether [NCT03800875].

3.2 Metformin

Metformin was approved for adults with T2D in 1994 and children T2D 10 years of age and older in 2000 [42]. In clinical practice, it is occasionally used off-label as an adjunctive therapy for T1D, especially in patients who are overweight or obese. However, evidence suggests that it has marginal benefits at best in lowering A1c levels in T1D. In a systematic review of metformin as an adjunctive treatment in adults with T1D, it was associated with a statistically significant reduction in totally daily insulin dose (6.6 units/day), but not in A1c [43]. Moreover, in a 3-year, randomized, placebo-controlled trial of metformin in 428 adults with T1D, there was no reduction in carotid intimal media thickness and no significant changes in insulin requirements, endothelial function, or retinopathy; only a 0.13% lowering of A1c was observed with metformin [44]. Limited efficacy of metformin as adjunctive

treatment of overweight adolescents with T1D was also demonstrated in the relatively large pediatric trial carried out by the Type 1 Diabetes Exchange (T1DX). In that study, 140 overweight adolescents with T1D were randomized to adjunctive treatment with metformin or placebo. While there were modest reductions in body weight and total daily doses of insulin in the metformin group after 26 weeks, there was no difference in A1c levels. On the other hand, hypoglycemia and gastrointestinal side effects were more common with metformin [45]. Taken together, these studies indicate that there is little benefit of metformin as adjunctive therapy to improve glycemic control in T1D.

3.3. Glucagon-like Peptide 1 (GLP-1) Receptor Agonists and Dipeptidyl Peptidase-4 inhibitors (DPP-4 inhibitors)

GLP-1 is a peptide hormone secreted from the endocrine L-cells in the intestine in response to ingesting a meal [46]. Similar to amylin, GLP-1 slows gastric emptying, inhibits glucagon release, and reduces appetite [47]. GLP-1 is rapidly degraded by DPP-4, making its half-life extremely short. GLP-1 receptor agonists, including liraglutide, were developed to maintain a longer half-life in the circulation than native GLP-1; namely, ~13 hours [48]. In a randomized, double-blind placebo controlled trial in 40 normal weight participants with suboptimal control of T1D, those with 12 weeks of liraglutide treatment had an overall reduction in A1c that was not significantly different than what was seen in the placebo group [49]. Other studies of GLP-1 agonist treatment in those with T1D have reported some lowering of insulin doses and body weight, but no significant changes in the frequency of hypoglycemic events or A1c levels [40,50]. As noted above, we have shown that the ability of GLP-1 agonists to slow gastric emptying and inhibit glucagon secretion wanes rapidly during treatment of T1D, which may help explain why improved metabolic control of T1D was not observed. As loss of appetite and weight loss may be the only benefits of GLP-1 agonists as adjunctive treatments for T1D, studies to gain regulatory approval for this indication are not being pursued by industry.

Since GLP-1 agonists appear to provide little benefit as adjunctive treatments of T1D besides appetite suppression and weight loss, it is predictable that DPP-4 inhibitors would have even less benefit, since they are weight neutral when used in treating T2D. Thus, it is not surprising that a meta-analysis of 6 randomized controlled trials showed no effect on A1c levels and a more recent metanalysis of pooled data from 5 randomized controlled trials indicated that there was no significantly lowering of A1c when DPP-4 inhibitors were used adjunctively with insulin [51].

3.4 Sodium-glucose Cotransporter-1/2 inhibitors (SGLT-1/2i) and Sodium-glucose Cotransporter-2 Inhibitors (SGLT-2i)

The kidneys play a key role in regulating glucose levels in the body. After filtration of blood in the glomeruli, plasma glucose passes through to the proximal tubule. In the proximal tubule, sodium glucose co-transporters mediate the transfer of 90% of glucose from the lumen back into the bloodstream [52]. By inhibiting SGLT-2 and preventing the reabsorption of glucose in the nephron, increased glucose is lost as glucosuria and plasma glucose levels will be reduced.⁵³ Using this insulin-independent mechanism, there is the potential to reduce hyperglycemic exposure, while simultaneously lowering total daily insulin doses in T1D.

Three SGLT-2 inhibitors (canagliflozin, dapagliflozin, ertugliflozin, and empagliflozin) were approved by the FDA for use in adults with type 2 diabetes in 2013 and several groups have evaluated the efficacy and safety of SGLT2i in adults with T1D [54]. Chen conducted a meta-analysis of trials with SGLT2i as adjunctive therapy for patients with T1D. A total of 7 clinical trials and 581 patients were included in the analysis [55]. In those studies, SGLT2i lowered A1c by 0.37%, body weight by 2.54 kg, and total daily dose of insulin by 6.22 units/day. A subsequent meta-analysis of prospective, randomized, placebo-controlled trials evaluating 14 studies that included 4591 subjects, also showed reductions in A1c by 0.4%, body weight by 2.68 kg, bolus and basal insulin doses by 3.6 u/day and 4.2 units/day, respectively and systolic blood pressure by 3 mmHg [56]. CGM studies showed decreased average glucose levels and lower glucose variability [56]. It is also noteworthy that studies in adults with T2D showed that empagliflozin had beneficial effects on heart failure and cardiovascular mortality. Additional studies are needed to see if these benefits extend to the T1D population.

It is particularly noteworthy that enthusiasm for use of SGLT2i has been dampened by reports of “euglycemic DKA” in patients with both T1D and T2D. T1D patients using insulin pumps would appear to be at greatest risk for DKA because they do not take long-acting insulin and often experience infusion site failures. We have recently shown that early metabolic decompensation resulting in increased circulating β -hydroxybutyrate levels during treatment of T1D with SGLT2i is not due to accelerated ketogenesis; what was observed was a slow and blunted rise in plasma glucose levels, undoubtedly due to increased urinary glucose excretion [57]. In current clinical practice, few T1D patients routinely measure blood or urine ketone levels; instead they rely on marked and persistent elevations in plasma glucose to recognize impending DKA. A recent consensus conference on mitigating the risks of DKA in patients treated with SGLT2i emphasized the need to monitor ketone levels regularly and to recognize the early symptoms of elevated ketone levels; namely nausea, abdominal discomfort and vomiting. Unfortunately, too many T1D patients fail to recognize that blood ketone levels are increasing even in the absence of SGLT2i treatment. Thus, the benefits of SGLT2i treatment in T1D may not be worth the risks, at least in the subset of poorly controlled patients who may need these drugs the most. Yet, to extend the use of these agents in the insulin requiring T2D and insulin dependent T1D populations, recent guidelines for management of ketosis in the setting of SGLT2 use have been developed⁵⁸. It is possible by using a non-glucocentric approach and teaching patients on these therapies to be diligent with ketone testing, this agent can successfully be employed in the treatment of both T1D and T2D.

Combined SGLT-1/2 inhibitors are currently undergoing FDA evaluation for the treatment of T1D. SGLT-1/2i not only prevents reabsorption of glucose in the kidneys, but also inhibits glucose absorption from the small intestine [59]. Interestingly, SGLT1 mediated glucose transport in the kidney is activated when the glucose exceeds the ability of the SGLT2 to reabsorb glucose. The inTandem1 study was a double-blind 52-week phase 3 trial comparing 200 mg and 400 mg of sotagliflozin to a placebo over 52 weeks. Those treated with sotagliflozin were not only satisfied with the treatment based on Diabetes Treatment Satisfaction Questionnaires, but also had significant decreases in weight (~4kg decrease), total insulin dose, and fasting plasma glucose levels. Additionally, reductions in A1c for the

200mg and 400mg sotagliflozin doses were 0.25% and 0.31%, respectively, at 52 weeks [60]. DKA rates in each group were 3.4% and 4.2% of patients receiving 200mg and 400 mg of sotagliflozin, respectively [60]. Additionally, in a phase 3 double-blind trial including those with T1D, 1402 patients received either 400mg sotagliflozin or placebo for 24 weeks. In the sotagliflozin group, A1c decreased by 0.46%, weight decreased by 2.98 kg, systolic blood pressure decreased by 3.5 mm Hg, and mean daily bolus dose of insulin decreased by 2.8 units when compared to controls [61]. Rates of severe hypoglycemia were similar between groups, however DKA was higher in the sotagliflozin group (3% compared to 0.6%). Overall, this suggests that with careful patient selection and education regarding a slightly higher risk of DKA, SGLT-1/2i's lead to metabolic health benefits in those with T1D.

4. Conclusion

Improvements in insulin therapy have allowed patients to have more control over their daily lives, but with this increase in control has also come the increased need to modify insulin doses on a frequent basis to keep up with changes in daily life, including stress, exercise, and illness. While there are many adjunctive diabetes treatment options available today, there are few that have shown significant decreases in A1c in clinical trials. When evaluating these options, it is important to focus on the individual needs of the patient, discuss the risks and benefits of each treatment carefully and work together to come to a decision about what treatment will be most beneficial. Most importantly, health care providers may need to broaden their treatment goals to move beyond A1c to metrics more relevant to patients living with this chronic condition including time in target range, body weight, and reducing burden of achieving targeted glycemic control [62]. A brief review of the potential uses, side effects, and cautions for recently approved insulins and adjunctive therapies are reviewed in tables 1 and 2.

5. Expert Opinion

With a plethora of medications available to provide targeted control of many aspects of pathophysiology related to T1D, specific treatment plans should be carefully chosen based on each patient's individual needs. At this time, faster acting insulin analogues are able to increase the rapidity of insulin absorption into the bloodstream, mitigating postprandial hyperglycemia, with the potential to improve quality of life for those with T1D. For those using continuous glucose monitoring, real-time glucose information can be overwhelming for patients and families managing T1D. Thus, even small decreases in glucose excursions and more rapid correction of hyperglycemia can lead to improved diabetes satisfaction. Shortening of the duration of action for these medications could also decrease rates of unwanted hypoglycemia several hours after eating, once digestion of food is complete. Further studies are needed to evaluate how insulin doses may change over time with these faster on, faster off therapies. Using these insulins in pump therapy could potentially lead to more rapid accumulation of ketones with infusion set failures because of the shorter duration of action when compared to current fast-acting insulin analogs.

Likewise, longer-acting basal insulins have the potential of reducing diabetes burden by decreasing the number of injections that need to be given, with the possibility of reducing risk of ketone formation with missed doses. However, it is uncertain if changing from a daily to every-other-day or once-weekly basal insulin will cause more missed doses. Careful consideration of each patient's needs and adherence should be taken into consideration.

Regarding adjunctive therapies, benefits are limited for GLP-1 agonists, DPP-4 inhibitors, metformin, and amylin analogs. With any adjunctive therapy, adherence is required on behalf of the patient, thus patients struggling with adherence to an insulin regimen alone may not benefit from adjunctive therapy. It is extremely important to carefully consider each patient's needs, motivation, consistency with their insulin regimen, and the potential benefits that treatment may provide. Adding an amylin analog, GLP-1 agonist, or DPP-4 inhibitor could promote small amounts of weight loss, but there is little evidence to suggest these will markedly improve A1c levels, leaving expectations modest at best. Total daily doses of insulin may decrease, and thus closer monitoring and follow up is recommended any time these medications are added to an insulin regimen. However, the increased psychological burden of adding another treatment to their diabetes therapy, potential for non-compliance by creating a more complicated regimen, and increased costs and expectations should be thoughtfully discussed with the patient.

SGLT inhibitors are appealing as an oral therapy with potential benefits of improved A1c, reductions in total insulin doses and potential for weight loss. However, patients with T1D who use these medications should be cautioned about the risk of developing diabetic ketoacidosis in the absence of drastic or prolonged hyperglycemia. Education about ketone checking needs to be explicitly provided for patients using these medications, especially in cases of illness or missed insulin doses, and may need to be performed on a more routine basis.

Funding

This paper was not funded.

Reviewer Disclosures

A reviewer on this manuscript has disclosed being on the Advisory Board for Lilly, NovoNordisk, Intarcia. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

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Article Highlights:

- The management of T1D has transformed dramatically over the past century from having only 1 type of insulin that was derived from animals to making human insulin using recombinant DNA technology.
- Due to the need for a faster, more potent onset of action, ultrafast insulin analogues and inhaled insulins have been clinically used for T1D to prevent postprandial hyperglycemia and mimic physiologic insulin secretion.
- Likewise, ultralong basal insulin analogues were developed to more closely match physiologic insulin secretion and create a flatter pharmacodynamic profile without a substantial action peak.
- Multiple therapies have been developed for the treatment of T2D, and studies to evaluate the potential clinical benefits those T1D are reviewed here.

Table 1.

Benefits, potential uses, cautions, and side effects of recently FDA-approved insulins.

Insulin Type	Benefits	Potential Use	Cautions	Side Effects
Insulin Human Inhalation Powder [19]	Rapid on, rapid off mitigate postprandial hyperglycemia	Hyperglycemia correction, prandial insulin dosing, patients with lipodystrophy or needle phobia	Spirometry (FEV1) prior to use, then every 6–12 months, contraindicated in chronic lung disease & active lung cancer, caution use in those who smoke, severe hypoglycemia	Bronchospasm, hypoglycemia, throat pain/irritation
Fast-acting insulin aspart [11,12,13]	Rapid on, rapid off	Hyperglycemia correction, prandial insulin dosing, may be given within 20 minutes of the start of a meal	Severe hypoglycemia	Hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, weight gain
Glargine U300 [25]	Duration of action > 24 hours, can be given at any time during the day rather than the same time each day	Patients who have difficulty remembering to take insulin at the same time each day	Titrate dose no more frequently than every 3–4 days to minimize risk of hypoglycemia, a higher daily dose may be needed than Glargine U100 insulin	Hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritis, rash edema, weight gain
Degludec [30]	Duration of action > 24 hours, can be given at any time during the day rather than the same time each day, pediatric patients	Patients who have difficulty remembering to take insulin at the same time each day, those needing greater than 80 units of basal insulin each day (up to 160 units in a single dose), those who experience pain with insulin injections (physiologic pH)	Titrate doses no more frequently than every 3–4 days to minimize risk of hypoglycemia, doses should be given no less than 8 hours apart, no conversion needed between U100 and U200 insulins	Hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritis, rash, edema, weight gain

Table 2.

Benefits, potential uses, cautions, and side effects of adjunctive therapies for type 1 diabetes.

Adjunctive Therapy	Benefits	Potential Use	Cautions	Side Effects
Pramlintide [35–41]	Lower A1c, weight loss in overweight/obese	Reduction of postprandial hyperglycemia, use in overweight/obese patients with T1D	May worsen gastroparesis, may require decreases in prandial insulin doses to avoid hypoglycemia, use with caution in those with hypoglycemia unawareness	Nausea, vomiting, anorexia, headache, slow dose titration and administration with food recommended to avoid side effects
Metformin [42–45]	Marginally lowers A1c, modest reduction in body weight for adolescents	Obese/overweight patients with T1D	Lactic acidosis in renal dysfunction, B12 deficiency with long-term use, hypoglycemia in adolescents, may require decreases in insulin doses to avoid hypoglycemia	Diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, headache
Liraglutide [49–50,64]	Weight reduction, lower TDD insulin	Obese/overweight patients with T1D	Use with caution in patients with thyroid cancer, may cause hemorrhagic or necrotizing pancreatitis, may need to decrease insulin doses to avoid hypoglycemia	Nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation.
Sodium/Glucose cotransporter Type 2 inhibitor [54–61,65]	Lower A1c, weight loss, decreased systolic blood pressure, lower TDD insulin, less glucose variability	Patients with T1D knowledgeable on signs/symptoms of ketosis, willing to check ketone levels regularly, and are aware of risk of DKA	Euglycemic DKA, need for urine/blood ketone monitoring in patients with T1D, may need to decrease insulin doses to avoid hypoglycemia	Polyuria, UTI, yeast infections