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# Newer Drugs for Type 2 Diabetes: An Emerging Adjunctive Therapy to Insulin for Type 1 Diabetes?

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## Summary

- There are two major categories of diabetes. Type 1 diabetes (T1D) is characterized by severe impairment or an absolute deficiency of insulin due to autoimmune destruction of pancreatic cells. Type 2 diabetes (T2D) is characterized by a combination of insulin resistance and decreased insulin secretion.
- Insulin is the mainstay of treatment for T1D. However, it may be difficult for some patients to reach target glycated hemoglobin (A1C) levels on insulin monotherapy. In some cases, hypoglycemia, excessive glucose fluctuations, and weight gain may also occur with intensive insulin therapy.
- Phase II-IV clinical trials have investigated the use of glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter-2 (SGLT-2) inhibitors, and dual sodium glucose transporter-1 and sodium glucose transporter-2 (SGLT-1/SGLT-2) inhibitors as adjunctive therapy with insulin for adult patients with T1D. Available data suggest that these drugs may reduce A1C by 0.1 to 0.6% and total daily insulin dose by 1 to 25 units per day, although combining insulin with some of the DDP-4 inhibitors or GLP-1 agonists did not appear to provide additional benefit in some studies. All of these drugs, with the exception of DPP-4 inhibitors, also appear to reduce weight by 0.3 to 6.8 kg, depending on the drug and dose used. Notably, these results are mostly based on preliminary data, and further studies are warranted to determine the true effect of these drugs.
- At this time, GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, and SGLT-1/SGLT-2 inhibitors may be considered experimental drugs being tested for adjunctive therapy in T1D adult patients. As such, their place in therapy in the management of T1D still needs to be defined.


## Background

Diabetes mellitus is a metabolic disorder that results from defects in insulin secretion, insulin action, or both.[1] There are two major categories of diabetes. Type 1 diabetes (T1D) is characterized by severe impairment or an absolute deficiency of insulin due to autoimmune destruction of pancreatic cells.[2,3] Type 2 diabetes (T2D) is characterized by a combination of insulin resistance and decreased insulin secretion.[1,3]

Hyperglycemia is the characteristic clinical sign of diabetes.[4] Chronic hyperglycemia can cause microvascular complications (e.g., diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy) and macrovascular complications (e.g., heart attack, stroke, and insufficiency in blood flow to the extremities).[5] Rates of hospitalization for cardiovascular disease and end-stage renal disease in individuals with diabetes are more than three and 12 times the rates seen in individuals without diabetes, respectively.[6] Complications associated with diabetes can result in premature death.[6,7] Diabetes has been attributed to an estimated 3.1% to 10% of deaths in Canada.[6,7] Diabetes is reported to be the seventh leading cause of death in Canada, and the economic impact of diabetes is $9 billion per year.[8]

In Canada, the prevalence of diabetes appears to be increasing. A recent report from Statistics Canada indicates that, in 2014, 6.7% of Canadians 12 years and older had diabetes (approximately 2 million people).[9] Diabetes Canada (formerly named The Canadian Diabetes Association) estimates that 9.2% of Canadians had diabetes in 2016.[7] The prevalence is expected to increase further to 11.6% by 2026.[7] Among individuals developing diabetes, about 90% will have T2D. T2D is one of the fastest-growing diseases in Canada, with more than 60,000 new cases yearly.[8] The proportion of diabetic patients with T1D is approximately 10%.[3]

Insulin is the mainstay of treatment for T1D.[10] Intensive glucose control has been associated with significant decreases in complications in T1D patients.[11] However, in some cases, it may be difficult for patients to reach target A1C levels on insulin monotherapy.[11] Some patients may also experience hypoglycemia, excessive glucose fluctuations, and weight gain with intensive insulin therapy.[2,11-13] However, adjunctive antihyperglycemic medications could play a role in improving glycemic control, possibly without increasing body weight or the risk of hypoglycemia.

## The Technology

This report discusses three recent drug classes that are primarily intended for the treatment of patients with T2D but also being studied for the treatment of those with T1D. It also discusses an emerging class of oral drugs currently being investigated for the treatment of patients with T1D.

### Glucagon-Like Peptide-1 Agonists

Glucagon-like peptide-1 (GLP-1) is produced in the intestine and released after the ingestion of food.[2] GLP-1 enhances glucose-induced insulin secretion by increasing the glucose sensitivity in pancreatic islet cells.[14,15] GLP-1 also has other effects, such as delaying the gastric-emptying rate,[14-16] increasing satiety,[16] and inhibiting glucagon secretion from pancreatic alpha cells during hyperglycemic episodes.[14,15]

In T2D, GLP-1 agonists have been shown to improve glycemic control (e.g., reduce A1C), decrease weight, and reduce insulin dose required.[1,17,18] These results are likely explained by the ability of GLP-1 receptor agonists to induce satiety, enhance glucose-induced insulin secretion, inhibit glucagon secretion, and slow gastric emptying.[18,19]

Similarly, GLP-1 agonists may be beneficial in the treatment of T1D through its ability to lower glucose levels by slowing gastric emptying, increase satiety, and suppress glucagon levels in the postprandial state.[2,14,20,21] In T1D patients with residual insulin production, GLP-1 agonists could potentially reduce plasma glucose excursions in the postprandial state by enhancing endogenous insulin secretion.[2]

### Dipeptidyl Peptidase-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that deactivates GLP-1 and glucose-dependent insulinotropic peptide (GIP).[1] Both GLP-1 and GIP are hormones that increase glucose-sensitive insulin secretion.[15] GLP-1 is also able to reduce glucagon secretion in hyperglycemia, whereas GIP increases glucagon secretion in hypoglycemia.[15] DPP-4 inhibitors reduce blood sugar levels by blocking DPP-4, thus preventing the inactivation of GLP-1 and GIP, which prolongs their meal-induced increases.[22] This leads to stimulation of the release of insulin in a glucose-dependent manner, satiety, and suppression of the release of glucagon after a meal.[1,11,22] In T2D patients, DPP-4 inhibitors have been shown to reduce A1C[1] and are generally well-tolerated.[23] DPP-4 inhibitors' mechanism of action is not solely dependent on insulin secretion, so it may also help with glycemic control in T1D patients.

### Sodium Glucose Cotransporter-2 Inhibitors

Sodium glucose cotransporter-2 (SGLT-2) is a protein expressed in the proximal convoluted tubule of the kidney. SGLT-2 plays a key role in reabsorbing filtered glucose.[12] SGLT-2 inhibitors block the reabsorption of glucose in the kidneys and induce glycosuria.[12,20] This process subsequently causes mild osmotic diuresis and net caloric loss.[13]

In T2D patients who use insulin, SLGT2 inhibitors have been shown to reduce A1C and weight without a significant increase in hypoglycemia.[12,24,25] T1D patients may also potentially benefit from SGLT-2 inhibitors as adjunctive therapy because SGLT-2 inhibitors' mechanism of action is independent of insulin secretion.[13]

### Dual Sodium Glucose Transporter-1 and Sodium Glucose Transporter-2 Inhibitors

Sodium glucose transporter-1 (SGLT-1) is the primary transporter in the intestine through which glucose and galactose are absorbed.[12,26] SGLT-1 is also responsible for approximately 10% of glucose reabsorption in the kidneys.[12] Inhibition of SGLT-1 reduces glucose absorption in the intestine, which leads to reduced postprandial glycemic excursions. SGLT-1 may also aid in weight and appetite control by stimulating the release of GLP-1 and polypeptide tyrosine tyrosine.[12,26] Sotagliflozin is an oral investigational dual SGLT-1/SGLT-2 inhibitor with a 20-fold selectivity for SGLT-2 over SGLT-1.[26] This drug is currently being investigated for the treatment of patients with T2D[27] as well as for the treatment of patients with T1D.[28] In T1D patients, SGLT-1/SGLT-2 inhibitors may improve glycemic control by reducing glucose absorption and promoting the release of GLP-1.[12]

## Regulatory Status

GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors have been approved in Canada for treatment of T2D (mostly used as second- and third-line agents). DPP-4 inhibitors and SGLT-2 inhibitors have also been approved as fixed-dose combination drug products with metformin.[29] Single-entity products that are available in Canada are listed in Table 1. No drug from these three classes is currently approved in Canada for T1D. There are other similar drugs available in other jurisdictions or in clinical development. For example, vildagliptin (Galvus, manufactured by Novartis) is a DPP-4 inhibitor approved in the European Union in 2008 for the treatment of patients with T2D, although its use is associated with adverse effects to the liver.[30] However, this drug is not approved in Canada or the US.[29,31] Another DPP-4 inhibitor in clinical development for the treatment of T2D is dutogliptin.[11] Semaglutide, a GLP-1 agonist used for treating patients with T2D, is also currently in clinical development.[32]

SGLT-1/SGLT-2 inhibitors are currently still under investigation and are not available on the market.[33] An example mentioned before is sotagliflozin, which is manufactured by Lexicon Pharmaceuticals Inc. Thus, neither the FDA nor Health Canada has approved the use of sotagliflozin.[29,31]

## Table 1: GLP-1 Agonists, DPP-4 Inhibitors, and SGLT-2 Inhibitors Available in Canada

| Drug Class | Drug (Trade Name and Manufacturer) |
|---|---|
| Glucagon-like Peptide-1 Agonists (GLP-1 Agonist) | Albiglutide (Eperzan, GlaxoSmithKline, Inc.) |
| | Dulaglutide (Trulicity, Eli Lilly Canada Inc.) |
| | Exenatide (Byetta, AstraZeneca Canada Inc.) Exenatide extended-release (Bydureon, AstraZeneca Canada Inc.) |
| | Liraglutide (Victoza, Novo Nordisk Canada Inc.) |
| | Lixisenatide (Adlyxine, Sanofi-Aventis Canada Inc.) |
| Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitors) | Alogliptin (Nesina, Takeda Canada Inc.) |
| | Linagliptin (Trajenta, Boehringer Ingelheim Canada Ltd.) |
| | Saxagliptin (Onglyza, AstraZeneca Canada Inc.) |
| | Sitagliptin (Januvia, Merck Canada Inc.) |
| Sodium Glucose Cotransporter-2 (SGLT-2 Inhibitors) | Canagliflozin (Invokana, Janssen Inc.) |
| | Dapagliflozin (Forxiga, AstraZeneca Canada Inc.) |
| | Empagliflozin (Jardiance, Boehringer Ingelheim Canada Ltd.) |

Note: Table adapted from Table 7 in Endocrine and Metabolic Disorders: Diabetes Mellitus Chapter of Therapeutic Choices. © Canadian Pharmacists Association, 2016. All rights reserved. Source: http://www.e-therapeutics.ca/. Accessed: November 30, 2016.

Other information sources include the Government of Canada Notice of Compliance Database[29] and the Government of Canada Drug and Health Product Register.[34]

## Patient Group

Insulin is a life-saving drug for T1D patients.[10] However, some T1D patients have difficulty obtaining glycemic control[18,25] on insulin due to the risk of severe hypoglycemia, the demanding nature of strict glycemic control, and the potential paradoxical increase in glucagon.[10,16,18] In some T1D patients, insulin use, along with dysfunctional counter-regulatory response, may contribute to hypoglycemia.[1,35] It is estimated that T1D patients experience a mean of two hypoglycemic episodes per week;[10] however, the majority of cases are non-severe.[36,37] Longitudinal studies have suggested that 4% to 10% of deaths in individuals with T1D are caused by hypoglycemia.[26] Use of insulin may also cause a weight gain of approximately 4.6 kg over a period of 10 years,[1,16,18] and weight gain tends to be related to daily insulin dose.[1] Excessive weight is a risk factor for cardiovascular complications and is associated with insulin resistance.[1,17,38]

## Current Practice

Therapy for most T1D patients should be targeted to achieve an A1C of 7.0% or less.[23,39] Targeting an hemoglobin A1C ≤ 7.0% can reduce the risk of microvascular and macrovascular complications.[23,39] In order to achieve an A1C of 7.0% or less, fasting plasma glucose (FPG) should be between 4.0 mmol/L and 7.0 mmol/L, and two-hour postprandial glucose should be between 5.0 mmol/L and 10.0 mmol/L.[39]

Insulin is the mainstay of management for T1D,[10,23] and it is the only drug class approved for the treatment of T1D in Canada.[10] Intensive insulin treatment has been shown to reduce the onset and/or progression of microvascular and macrovascular complications.[13,23] Insulin is administered subcutaneously either through multiple daily injections using a syringe or pen or as a continuous subcutaneous insulin infusion using a pump.[10] Many

insulin preparations are available in Canada with varying durations of action, times of onset, and times of peak action.[10] In addition to insulin therapy, patients are encouraged to implement lifestyle interventions, such as dietary and activity modifications.[1,10]

National diabetes guidelines, including those from Diabetes Canada, have acknowledged that there may be a role for adjunctive therapy in some T1D patients.[10,23,40] In the US, pramlintide acetate injection (Symlin) is the only noninsulin drug approved for adjunctive treatment of T1D.[13,29] Metformin, a T2D medication, is mentioned by Diabetes Canada and the American Diabetes Association for off-label use to reduce insulin requirements and total cholesterol/low-density lipoprotein ratios,[10,17,23] with the caveat that it does not improve hemoglobin A1C.[10,23] The National Institute for Health and Care Excellence guidelines also mention metformin as adjunctive therapy to insulin for T1D patients, but only for patients with a BMI ≥ 25kg/m$^2$ (≥ 23 kg/m$^2$ for people from South Asian and related minority ethnic groups).[40] Regarding other adjunctive drugs, the American Diabetes Association acknowledges that GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors are investigational agents for T1D.[23]

## The Evidence

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and the Cochrane Library (2016, Issue 11). Grey literature was identified by searching relevant sections of the *Grey Matters checklist* (https://www.cadth.ca/grey-matters). Methodological filters were applied to limit retrieval to randomized controlled trials and clinical studies. The search was limited to English-language documents published between January 1, 2009 and October 26, 2016. Regular alerts were established to update the search until September 14, 2017.

Published clinical trials investigating the use of GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, and one SGLT-1/SGLT-2 inhibitor are listed in Tables 2, 3, 4, and 5, respectively. Studies involving only patients with latent autoimmune diabetes or diabetes as a complication from renal transplantation were excluded. Studies using only a closed-loop system to deliver insulin or concomitant administration of daclizumab were also omitted. The phase of each trial was retrieved from the published article or from ClinicalTrials.gov (https://clinicaltrials.gov/), if it was not stated in the article. In this report, the effects of adjunctive therapy on A1C, total daily insulin dose, and weight are the key end points. The duration listed in the tables refers to the time during which patients received each treatment, and the number of patients listed is the total number of patients randomized in the trial. Standard deviation, standard error, and confidence intervals (CIs) are reported, where available. *P* values are included in the tables if statistical testing was performed and differences were statistically significant. Results for intergroup comparisons are reported where available, and when unavailable, within-group comparisons are reported.

### GLP-1 Agonists

In addition to the published studies (Table 2), there were three conference abstracts identified that reported on unpublished studies investigating the use of GLP-1 agonists for T1D patients.[44-46]

Alattar et al. presented findings from a crossover study (6 months on and 6 months off exenatide) of 14 subjects with a T1D mean duration of 20.2 years.[46] Analysis showed no statistically significant change in A1C or daily insulin requirement with the addition of exenatide compared with insulin monotherapy.[46] However, FPG was reported to be higher during exenatide treatment (7.9 ± 0.2 versus 7.3 ± 0.2, $P < 0.0001$).[46]

Heller et al. presented a crossover study of 45 adults allocated to liraglutide (with doses of 0.6 mg, 1.2 mg, and 1.8 mg) and placebo for four weeks.[45] There was no change in A1C in the liraglutide groups compared with the group receiving the placebo.[45] However, there was a significant decrease in daily insulin dose (up to 10.6 units) and weight (up to 3.7 kg) in patients who received liraglutide compared with those who received the placebo.[45]

Dandona et al. presented the findings of a randomized trial consisting of 32 patients allocated to liraglutide 1.8 mg daily or placebo for 12 weeks.[44] A1C decreased by 0.43% in the liraglutide group compared with 0.3% in the placebo group.[44] There was a 20% reduction in insulin dose in the liraglutide group but no change in the placebo group.[44] It is unknown whether these differences are statistically significant, as statistical testing was not reported.[44]

Results from another phase II/III trial of liraglutide in T1D patients, the Lira Pump Trial (The Effects of Liraglutide in Patients With Insulin Pump Treated Type 1 Diabetes: A Randomized Placebo-Controlled Trial), should soon be available. This study is investigating the effects of liraglutide as an add-on therapy in overweight T1D patients on an insulin pump who have suboptimal glycemic control.[47]

Overall, studies show that the addition of GLP-1 agonists to insulin may reduce A1C,[17,41,44,46] total daily insulin dose,[14,17-19,21,24,41] and weight[14,18] compared with insulin monotherapy. The effect of GLP-1 agonists on A1C was inconsistent between included studies.[14,18,19,45,46] In the studies that showed a difference in A1C, A1C decreased by 0.1% to 0.5% with liraglutide treatment compared with placebo.[17,41,44,46] Use of GLP-1 agonists reduced daily insulin requirements by approximately six to 25 units.[17,21,45] Of note, the large decrease in insulin dose seen in the Hari Kumar et al. study might not be replicable in Canadian practice, given the differences in population and clinical practice between North

America and India. The majority of studies suggest that the reduction in daily insulin dose was mainly a result of a decrease in bolus insulin.[17-19,48] Weight reduction was seen in both normal-weight[14,18] and overweight patients.[17] Weight loss with GLP-1 agonist was approximately 2.5 kg to 5 kg.[14,17,18,21,41]

Of interest, a recent meta-analysis by Panta et al. reported that, compared with placebo, the use of liraglutide for 12 weeks in 212 patients with T1D was associated with a 0.29% reduction (95% CI, −0.52 to −0.06) in A1C. The use of liraglutide was also associated with a 4.39 unit reduction in daily bolus insulin (95% CI, −6.28 to −2.49) and a daily decrease of 2.55 units in basal insulin (95% CI, −4.87 to −0.22). In addition, a 4.56 kg weight loss (95% CI, −5.42 to −3.7) was reported. However, the authors indicated that results from the ADJUNCT ONE and ADJUNCT TWO trials were not included in their meta-analysis.[49,50] Another recent meta-analysis

## Table 2: Clinical Trials for GLP-1 Agonists

| Study | Study Design/Intervention/ Comparator/Duration | Key Findings |
|---|---|---|
| Exenatide<br>Hari Kumar et al. 2013[21]<br>N = 18 | *Design*<br>Phase IV, randomized, open-label study<br>*Patient Population*<br>Patients aged > 18 years, newly diagnosed with T1D and positive for ketones and GAD antibodies<br>*Interventions*<br>Exenatide 5 mcg SC b.i.d. x 1 month, then 10 mcg SC b.i.d. onwards + insulin<br>Sitagliptin 100 mg P.O. daily + insulin<br>*Comparison*<br>Insulin monotherapy<br>*Duration*<br>52 weeks | Change in total daily insulin dose from baseline to 52 weeks (1° outcome) — *mean (SD), units*<br>Exenatide + insulin: −39.2 (20.5)[a]<br>Sitagliptin + insulin: −23.7 (13.9)[a]<br>Insulin monotherapy: −15.2 (9.5)<br>Change in A1C from baseline to 52 weeks (2o outcome) — *calculated mean, %*<br>Exenatide + insulin: −2.3[b]<br>Sitagliptin + insulin: −2.1[b]<br>Insulin monotherapy: −2.0[b]<br>Change in weight from baseline to 52 weeks (2o outcome) — *calculated mean, kg*<br>Exenatide + insulin: −0.5<br>Sitagliptin + insulin: +2.7[b]<br>Insulin monotherapy: +4.0[b] |
| Liraglutide<br>Mathieu et al. 2016[17] ADJUNCT ONE<br>N = 1,398 | *Design*<br>Phase III, randomized, placebo-controlled, double-blind, parallel-group study<br>*Patient Population*<br>Patients aged 18 to 75 years who had had T1D for ≥ 12 months prior to the screening visit, treatment with multiple daily insulin injections or CSII for ≥ 6 months, and stable insulin treatment for the last 3 months, and who had a BMI of ≥ 20 kg/m$^2$<br>*Interventions*<br>Liraglutide 0.6 mg SC daily<br>Liraglutide 1.2 mg SC daily<br>Liraglutide 1.8 mg SC daily<br>*Comparison*<br>Placebo<br>*Duration*<br>52 weeks | Change in A1C from baseline to 52 weeks (1o outcome) — *mean, %*<br>Liraglutide 0.6 mg: −0.43<br>ETD −0.09 (95% CI, −0.21 to +0.03)<br>Liraglutide 1.2 mg: −0.49<br>ETD −0.15 (95% CI, −0.27 to −0.03)[a]<br>Liraglutide 1.8 mg: −0.54<br>ETD −0.20 (95%CI, −0.32 to −0.07)[a]<br>Placebo: −0.34<br>Change in total daily insulin dose from baseline to 52 weeks (1° outcome) — *mean, %*<br>Liraglutide 0.6 mg: +4<br>Liraglutide 1.2 mg:−2[a]<br>Liraglutide 1.8 mg: −5[a]<br>Placebo: +4<br>Change in weight from baseline to 52 weeks (1° outcome) — mean, kg<br>Liraglutide 0.6 mg: −1.3<br>ETD −2.19, (95% CI, −2.91 to −1.47)[a]<br>Liraglutide 1.2 mg:−2.7<br>ETD −3.55 (95% CI, −4.29 to −2.81)[a]<br>Liraglutide 1.8 mg:−4.0<br>ETD −4.90 (95% CI, −5.65 to −4.16)[a]<br>Placebo: +0.9 |

| Study | Study Design/Intervention/ Comparator/Duration | Key Findings |
|---|---|---|
| Liraglutide<br>Ahrén et al. 2016[41]<br>ADJUNCT TWO<br>N = 835 | *Design*<br>Phase III, randomized, double-blind, placebo-controlled, parallel-group study<br>*Patient Population*<br>Patients aged ≥ 18 years who had had T1D for ≥ 1 year, treatment with multiple daily insulin injections or CSII for ≥ 6 months, and a stable insulin dose for ≥ 3 months, and who had a A1C level of 7.0 to 10.0 % and a BMI of ≥ 20 kg/m2<br>*Intervention*<br>Liraglutide 0.6 mg SC daily<br>Liraglutide 1.2 mg SC daily<br>Liraglutide 1.8 mg SC daily<br>*Comparison*<br>Placebo<br>*Duration*<br>26 week | Change in A1C from baseline to 26 weeks (1° outcome) — *mean, %*<br>Liraglutide 0.6 mg: −0.23[a]<br>ETD: −0.24 (95% CI, −0.39 to −0.10)<br>Liraglutide 1.2 mg: −0.22[a]<br>ETD: −0.23 (95% CI, −0.38 to −0.08)<br>Liraglutide 1.8 mg: −0.33[a]<br>ETD: −0.35 (95% CI, −0.50 to −0.20)<br>Placebo: +0.01<br>Change in mean total daily insulin dose to 26 weeks (2o outcome) — *estimated treatment ratio (95% CI)*<br>Liraglutide 0.6 mg: −0.95 (0.92 to 0.99)[a]<br>Liraglutide 1.2 mg: −0.93 (0.90 to 0.96)[a]<br>Liraglutide 1.8 mg: −0.9 (0.86 to 0.93)[a]<br>Change in body weight from baseline to 26 weeks (2° outcome) — *mean, kg*<br>Liraglutide 0.6 mg: −2.5<br>Liraglutide 1.2 mg: −4.0<br>Liraglutide 1.8 mg: −5.1<br>Placebo: −0.2 |
| Liraglutide<br>Dejgaard et al. 2016[19]<br>Lira-1<br>N = 100 | *Design*<br>Phase IV, randomized, double-blind, placebo-controlled study<br>*Patient Population*<br>Patients aged ≥ 18 years who had had T1D for > 1 year and had a A1C level of > 8% and a BMI of > 25 kg/m2<br>*Intervention*<br>Liraglutide 0.6 mg SC daily x 1 week, then liraglutide 1.2 mg SC daily x 1 week, then liraglutide 1.8 mg SC daily onwards<br>*Comparison*<br>Placebo<br>*Duration*<br>24 weeks | A1C at week 24 (1° outcome) — *mean (95% CI), %*<br>Liraglutide: 8.2 (7.9 to 8.4)<br>Placebo: 8.4 (8.1 to 8.6)<br>Total daily insulin dose at week 24 (2° outcome) — *mean (95% CI), units*<br>Liraglutide: 62.8 (55.7 to 69.9)[a]<br>Placebo: 74.0 (66.9 to 81.1)<br>Body weight at week 24 (2° outcome) — *mean (95% CI), kg*<br>Liraglutide: 86.5 (82.7 to 90.3)[a]<br>Placebo: 93.3 (89.5 to 97.1) |
| Liraglutide<br>Frandsen et al. 2015[18,42]<br>T1DMLIRA<br>N = 40 | *Design*<br>Phase III, randomized, double-blind, placebo-controlled, parallel design study<br>*Patient Population*<br>Patients aged 18 to 70 years who had been diagnosed with T1D between the ages of 5 and 40 years; who had a A1C level of ≥ 8%, no residual beta-cell function, and a BMI of 18 to 28 kg/m2; and who were of Caucasian descent<br>*Intervention*<br>Liraglutide 0.6 mg SC daily x 1 week, then 1.2 mg SC daily onwards, if tolerated<br>*Comparison*<br>Placebo<br>*Duration*<br>12 weeks | Change in A1C from baseline to 12 weeks (1° outcome) — *mean ± SE, %*<br>Liraglutide: −0.6 ± 0.2<br>Placebo: −0.5 ± 0.2<br>Change in body weight from baseline to 12 weeks (2° outcome) — *mean ± SE, kg*<br>Liraglutide: −3.1 ± 0.6[a]<br>Placebo: +1.1 ± 0.4 |

| Study | Study Design/Intervention/ Comparator/Duration | Key Findings |
|---|---|---|
| Liraglutide<br>Kielgast et al. 2011[14]<br>N = 29 | *Design*<br>Phase II/III, modified randomized controlled, open-label study<br>*Patient Population*<br>Patients aged 18 to 50 years who had been diagnosed with T1D between the ages of 5 and 40 years; who had a A1C level of ≤ 8% and a BMI of 18 to 27 kg/m2; whose remission period was assumed to be ended; and who were of Caucasian descent and had no known late diabetes complications (except microalbuminuria) and no symptoms of autonomic neuropathy<br>*Intervention*<br>Liraglutide 0.6 mg SC daily x 1 week, then 1.2 mg SC daily onwards<br>(all 10 C-peptide positive patients and 9 C-peptide negative patients received liraglutide treatment)<br>*Comparison*<br>Insulin monotherapy<br>(10 C-peptide negative patients received insulin monotherapy)<br>*Duration*<br>4 weeks | Change in total daily insulin dose from baseline to 4 weeks (1° outcome) — *mean ± SE, units/kg*<br>Liraglutide (C-peptide-positive): −0.194 ± 0.03a<br>Liraglutide (C-peptide-negative): −0.13 ± 0.04a<br>Insulin monotherapy: +0.017 ± 0.02<br>Change in A1C from baseline to 4 weeks (2° outcome) — *mean ± SE, %*<br>Liraglutide (C-peptide-positive): −0.26 ± 0.1<br>Liraglutide (C-peptide-negative): −0.47 ± 0.15<br>Insulin monotherapy: − 0.18 ± 0.1<br>Change in body weight from baseline to 4 weeks (2° outcome) — *mean ± SE, kg*<br>Liraglutide (all patients): −2.3 ± 0.3[a]<br>Insulin monotherapy: + 0.2 ± 0.3<br>*Note: C-peptide is an indirect measurement of a patient's ability to produce insulin.*[16] |
| Liraglutide<br>Kuhadiya et al. 2016[43]<br>N = 72 | *Design*<br>Phase IV, randomized, placebo-controlled, parallel-group study<br>*Population*<br>Patients aged 18 to 75 years with T1D who were treated with multiple daily insulin injections or CSII and had a C-peptide of < 0.1 mmol/L and a A1C level of ≤ 8.5%<br>*Intervention*<br>Liraglutide 0.6 mg SC daily<br>Liraglutide 1.2 mg SC daily<br>Lirglutide 1.8 mg SC daily<br>*Comparison*<br>Placebo<br>*Duration*<br>12 weeks | Change in A1C from baseline to 12 weeks (2° outcome) — *mean ± SE, %*<br>Liraglutide 0.6 mg: −0.26 ± 0.17<br>Liraglutide 1.2 mg: −0.78 ± 0.15[a]<br>Liraglutide 1.8 mg: −0.42 ± 0.15<br>Placebo: −0.3 ± 0.15<br>Change in total daily insulin dose from baseline to 12 weeks (2° outcome) — *mean ± SE, units*<br>Liraglutide 0.6 mg: −2.8 ± 0.7<br>Liraglutide 1.2 mg: −12.1 ± 0.7[a]<br>Liraglutide 1.8 mg: −10.0 ± 0.5[a]<br>Placebo: −1.9 ± 0.7<br>Change in weight from baseline to 12 weeks (2° outcome) — *mean ± SE*, kg<br>Liraglutide 0.6 mg: −2.7 ± 0.6[a]<br>Lirglutide 1.2 mg: −5.0 ± 1.2[a]<br>Liraglutide 1.8 mg: −4.8 ± 0.7[a]<br>Placebo: −0.3 ± 0.5 |

1° = primary; 2° = secondary; A1C = glycated hemoglobin; b.i.d. = twice daily; BMI = body mass index; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; ETD = estimated treatment difference (change in treatment group - change in placebo group); FPG = fasting plasma glucose; GAD = glutamic acid decarboxylase; GLP-1 = glucagon-like peptide-1; P.O. = orally; SC = subcutaneously; SD = standard deviation; SE = standard error; T1D = type 1 diabetes.

[a]*P* < 0.05 compared with placebo/insulin monotherapy.

[b]*P* < 0.05 within-group comparison to baseline.

of seven trials evaluating the effect of adding a GLP-1 agonist to insulin therapy, versus the use of insulin monotherapy, was retrieved. It found that add-on therapy with a GLP-1 agonist results in a statistically significant reduction in i) A1C (mean difference = −0.21% [95% CI, −0.40 to −0.02]), ii) body weight (mean difference = −3.53 kg (−4.86, −2.19]), iii), and daily bolus insulin dosage (mean difference = −0.06 units/kg/day [−0.1, −0.02]), but not in total daily insulin dosage (mean difference = −0.11 units/kg/day [−0.23, 0.00]).[51] Only four of the seven studies listed in Table 2 were included in the meta-analysis by Wang et al. (2017);.[51]; Ahrén et al. (2016),[41] Mathieu et al. (2016),[17] and Kielgast et al. (2011)[14] are missing.

Studies have also investigated the effect of GLP-1 agonists on cardiovascular surrogate endpoints and quality of life.[14,17-19,41,43,46] Study results on GLP-1 agonists' effect on blood pressure and lipids were conflicting.[14,18,19,41,46] As TRIM-D total scores were significantly higher for all liraglutide groups compared with the placebo group, quality of life was improved with liraglutide adjunctive therapy.[17,41] However, there was no effect on any of the liraglutide groups compared with the placebo group in the Short-Form (36) Health Survey (SF-36) overall physical and mental scores.[17,41] Total treatment satisfaction scores did not differ between treatment with liraglutide and treatment with placebo.[19]

DPP-4 Inhibitors

## Table 3: Clinical Trials for DPP-4 Inhibitors

| Study | Study Design/Intervention/Comparator/Duration | Key Findings |
|---|---|---|
| Saxagliptin<br>George et al. 2016[35]<br>N = 14 | *Design*<br>Phase III, randomized, double-blind, placebo-controlled, crossover study<br>*Patent Population*<br>Adult patients who had had T1D for > 5 years and were C-peptide negative<br>*Intervention*<br>Saxagliptin 5 mg P.O. daily<br>*Comparison*<br>Placebo<br>*Duration*<br>12 weeks | Change in A1C from baseline to 12 weeks (2° outcome) — *presumed mean, mmol/L*<br>Saxagliptin: +0.3<br>Placebo: −1.6<br>Change in weight from baseline to 12 weeks (2° outcome) — *mean, kg*<br>Saxagliptin: +0.24<br>Placebo: +0.07<br>*Notes:*<br>*- Change in A1C was not available as % units.*<br>*- Investigators reported that there was no effect of saxagliptin on daily insulin dose, but numerical values of dose change were not available for verification.* |
| Sitagliptin<br>Ellis et al. 2011[52]<br>N = 20 | *Design*<br>Phase IV, randomized, double-blind, placebo-controlled, crossover study<br>*Patient Population*<br>Patients aged 18 to 70 years withT1D who had been receiving stable treatment with multiple daily insulin injection or CSII and who had an A1C level of 8.5% to 12%<br>*Intervention*<br>Sitagliptin 100 mg P.O. daily<br>*Comparison*<br>Placebo<br>*Duration*<br>4 weeks | Change in A1C from baseline to 4 weeks (2° outcome) — *estimated difference compared with placebo, least-square mean (SD), %*<br>−0.27 (0.11)[a]<br>Change in total daily insulin dose from baseline to 4 weeks (2° outcome) — *estimated difference compared with placebo, least-square mean (SD), units/kg*<br>−0.051 ± 0.18[a]<br>*Note: Investigators reported that there was no difference in weight between groups, but the numerical values of weight change were not available for verification.* |
| Sitagliptin<br>Hari Kumar et al. 2013[21] | *See Table 2 for description* | *See Table 2 for description* |

| Study | Study Design/Intervention/Comparator/Duration | Key Findings |
|---|---|---|
| Sitagliptin<br>Garg et al. 2013[22]<br>N = 125 | *Design*<br>Randomized, double-blind, placebo-controlled study (study phase not reported)<br>*Patent Population*<br>Patients aged 18 to 70 years who had had T1D for > 1 year, had been treated with either multiple daily insulin injections or CSII, had been on a stable insulin dose for ≥ 1 month, routinely tested blood glucose at least 2 to 4 times daily, and had an A1C level of between 7.5% and 10%, and a BMI of < 35 kg/m$^2$<br>*Intervention*<br>Sitagliptin 100 mg P.O. daily<br>*Comparison*<br>Placebo<br>*Duration*<br>16 weeks | Change in A1C from baseline to 16 weeks (2$^o$ outcome) — *mean (SD), %*<br>Sitagliptin: −0.07 (0.70)<br>Placebo: −0.12 (0.75)<br>Change in total daily insulin dose from baseline to 16 weeks (2$^o$ outcome) — *mean (SD), units*<br>Sitagliptin: −2.04 (11.45)<br>Placebo: +0.22 (9.17)<br>Change in weight from baseline to 16 weeks (2$^o$ outcome) — *mean (SD), kg*<br>Sitagliptin: +0.10 (3.92)<br>Placebo: +0.02 (2.67) |
| Vildagliptin<br>Farngren et al. 2012[15]<br>N = 29 | *Design*<br>Phase IV, randomized, double-blind, randomized, placebo-controlled, crossover study<br>*Patent Population*<br>Patients aged ≥ 18 years who had had C-peptide negative, antibody-positive T1D for 2 to 20 years and who had an A1C level of 6.5% to 8.5%<br>*Intervention*<br>Vildagliptin 50 mg P.O. b.i.d.<br>*Comparison*<br>Placebo<br>*Duration*<br>4 weeks | Change in hemoglobin A1C from baseline to 4 weeks (2$^o$ outcome) — *mean (SD),%*<br>Vildagliptin : −0.34 ± 0.10[a]<br>Placebo: −0.02 ± 0.07<br>*Note: Investigators reported that the dosage of insulin was not significantly altered, but no numerical values were available for verification.* |

A1C = glycated hemoglobin; BMI = body mass index; b.i.d. = twice daily; CSII = continuous subcutaneous insulin infusion; DPP-4 = dipeptidyl peptidase-4; P.O. = orally; SD = standard deviation; T1D = type 1 diabetes.

[a] *P* value < 0.05 compared with placebo.

In addition to the aforementioned studies (Table 3), a meta-analysis was retrieved (Guo et al.) that included six randomized controlled trials with either a parallel design or a crossover design of DPP-4 inhibitors and insulin versus placebo treatment.[11] This meta-analysis included all the studies described in Table 3, and an additional study by Zhao et al. that consisted only of patients with recent-onset latent autoimmune diabetes.[53] The meta-analysis reported no significant improvement in A1C with DPP-4 inhibitor treatment compared with placebo (inverse variance weighted mean difference = 0.0%, 95% CI, −0.16 to 0.15, $P$ = 0.97, $I^2$ = 17%), but it did report a reduction in daily insulin dose with the addition of DPP-4 inhibitors compared with placebo (weighted mean difference = −2.41 units/day, 95% CI, −3.87 to −0.97, $P$ = 0.001, $I^2$ = 0%). It also reported that there was no weight change between DPP-4 inhibitors and placebo (pooled statistical analysis not available). Limitations of this meta-analysis were the low-quality evidence of the original studies, the existence of clinical and methodological heterogeneity, and the inability to exclude publication bias.[11] Of note, the Zhao et al. study that included patients with latent onset diabetes showed no difference in A1C, and it was heavily weighted in this meta-analysis.[11,53] When only the studies in Table 3 are examined, there appears to be a small decrease in A1C.

The majority of trials listed in Table 3 reported that the addition of DPP-4 inhibitors to insulin may reduce A1C and total daily insulin dose, but it did not affect weight compared with insulin alone. In the trials that reported a statistically significant reduction in A1C, the decrease was approximately 0.1% to 0.3% versus insulin monotherapy.[15,21]

SGLT-2 Inhibitors

## Table 4: Clinical Trials for SGLT-2 Inhibitors

| Study | Study Design/Intervention/Comparator/Duration | Key Findings |
|---|---|---|
| Dapagliflozin<br>Henry et al. 2015[24,54]<br>N = 70 | *Design*<br>Phase IIa, randomized, double-blind, placebo-controlled, parallel-group study<br>*Patient population*<br>Patients aged 18 to 65 years with T1D who had been treated with multiple daily insulin injections or CSII for ≥ 12 months and had an A1C level of 7 to 10%<br>*Interventions*<br>Dapagliflozin 1 mg P.O. daily<br>Dapagliflozin 2.5 mg P.O. daily<br>Dapagliflozin 5 mg P.O. daily<br>Dapagliflozin 10 mg P.O. daily<br>*Comparator*<br>Placebo<br>*Duration*<br>14 days | Change in total daily insulin dose from baseline to day 7 (2° outcome) — *mean (95% CI), %*<br>Dapagliflozin 1 mg: −16.0 (−25.9 to −4.7)<br>Dapagliflozin 2.5 mg: −11.1 (−22.1 to +1.4)<br>Dapagliflozin 5 mg: −19.3 (−30.1 to −6.8)<br>Dapagliflozin 10 mg: −16.2 (−29.4 to −0.5)<br>Placebo: +1.7 (−22.8 to +33.9)<br>Change in body weight from baseline to day 7 (2° outcome) — *mean (95% CI), kg*<br>Dapagliflozin 1 mg: −1.05 (−2.07 to −0.03)<br>Dapagliflozin 2.5 mg: −0.30 (−1.24 to +0.64)<br>Dapagliflozin 5 mg: −0.89 (−1.39 to −0.39)<br>Dapagliflozin 10 mg: −0.66 (−1.39 to +0.07)<br>Placebo: +0.02 (−0.99 to +1.04)<br>*Note: Investigators reported that no P values were calculated.* |
| Dapagliflozin<br>Kuhadiya et al. 2016[20]<br>N = 30 | *Design*<br>Phase IV, randomized, double-blind, placebo-controlled study<br>*Patient population*<br>Patients 18 to 75 years of age with T1D who had a fasting C-peptide of < 0.1 nmol/L; who had been treated with multiple daily insulin injections or CSII for > 12 months and were on liraglutide therapy at maximal tolerated doses for ≥ 6 months; and who had an A1C level of ≤ 9.2%<br>*Intervention*<br>Dapagliflozin 10 mg P.O. daily<br>*Comparison*<br>Placebo<br>*Duration*<br>12 weeks | Change in mean A1C from baseline to 12 weeks (1° outcome) — *mean ± SE, %*<br>Dapagliflozin: −0.66 ± 0.08[a]<br>Placebo: 0 ± 0.2<br>Change in total insulin dose from baseline to 12 weeks (2° outcome) — *mean ± SE, units*<br>Dapagliflozin: −3.5 ± 1.9<br>Placebo: 0.1 ± 2.4<br>*Note: Authors did not indicate whether this result refers to total daily insulin dose*<br>Change in body weight from baseline to 12 weeks (2° outcome) — *mean ± SE, kg*<br>Dapaglifolzin: −1.9 ± 0.54[a]<br>Placebo: +0.7 ± 1.5 |
| Dapagliflozin<br>Dandona et al. 2017 (DEPICT-1)<br>N = 834[55] | *Design*<br>Phase III, multi-centre, double-blind, parallel-controlled, three-arm, randomized controlled study<br>*Patent Population*<br>Patients aged 18 to 75 years with inadequately controlled T1D ( A1C of ≥ 7.7% and ≤ 11.0%) who had been on insulin for at least 12 months before enrolment<br>*Interventions*<br>dapagliflozin 5 mg P.O. once daily<br>dapagliflozin 10 mg P.O. once daily<br>*Comparison*<br>Placebo<br>*Duration*<br>24 weeks | Change in A1C from baseline to 24 weeks — *mean difference (P value), %:*<br>dapagliflozin 5 mg: −0·42 (*P* <.0001)[a]<br>dapagliflozin 10 mg: −0·45 (*P* <.0001)[a]<br>Change in total daily insulin dose from baseline to 24 weeks — *mean difference (P value), %*:<br>dapagliflozin 5 mg: −8.8 (*P* <.0001)[a]<br>dapagliflozin 10 mg: −13.2 (*P* <.0001)[a]<br>Change in body weight from baseline to 24 weeks — *mean difference (P value), %*:<br>dapagliflozin 5 mg: −2.96 (*P* <.0001)[a]<br>dapagliflozin 10 mg: −3.72 (*P* <.0001)[a] |

| Study | Study Design/Intervention/Comparator/Duration | Key Findings |
|---|---|---|
| Canagliflozin<br>Henry et al. 2015[13]<br>N = 351 | *Design*<br>Phase II, randomized, double-blind, parallel-group study<br>*Patent Population*<br>Patients aged 25 to 65 years who had had T1D for ≥ 1 year, had a fasting C-peptide level of < 0.2 pmol/L, had been treated with a stable regimen of multiple daily insulin injections or CSII for ≥ 8 weeks, and had an A1C level of 7.0 to 9.0% and a BMI of 21 to 35 kg/m$^2$<br>*Interventions*<br>Canagliflozin 100 mg P.O. daily<br>Canagliflozin 300 mg P.O. daily<br>*Comparison*<br>Placebo<br>*Duration*<br>18 weeks | Proportion of patients with A1C reduction ≥ 0.4% and no increase in body weight at 18 weeks (1° outcome), %<br>Canagliflozin 100 mg: 36.9[a]<br>Canagliflozin 300 mg: 41.4[a]<br>Placebo: 14.5<br>[a]*< 0.001 for both comparisons vs. placebo*<br>Change in A1C from baseline to week 18 (2° outcome), %<br>Canagliflozin 100 mg: −0.27 (Δ −0.29 [95% CI, −.0.43 to −0.14])<br>Canagliflozin 300 mg: −0.24 (Δ −0.25 [95% CI, −0.40 to −0.11])<br>Placebo: +0.01<br>Change in total daily insulin dose from baseline to week 18 (2° outcome) IU/day<br>Canagliflozin 100 mg: −2.5 (Δ = −4.1 [95% CI, −7.9 to −0.3])<br>Canagliflozin 300 mg: −6.0 (Δ = −7.6 [95% CI, −11.3 to −3.8])<br>Placebo: +1.6<br>Change in body weight from baseline to 18 weeks (2° outcome), kg<br>Canagliflozin 100 mg: −2.6 (Δ −2.8 [95% CI, −3.5 to −2.1])<br>Canagliflozin 300 mg:−4.2 (Δ −4.4 [95% CI, −5.2 to −3.7])<br>Placebo: +0.2 |
| Empagliflozin<br>Pieber et al. 2015[25]<br>EASE-1<br>N = 75 | *Design*<br>Phase II, randomized, double-blind, placebo-controlled, parallel-group study<br>*Patent Population*<br>Patients aged 18 to 65 years of age with T1D who had been treated with multiple daily insulin injections consisting of basal and ≥ 3 daily bolus injections for ≥ 12 months; had a total insulin requirement of ≤ 1.5 units/kg/ day; had had a stable insulin algorithm for ≥ 12 weeks; and had a C-peptide of < 1.5 ng/mL, an A1C level of 7.5 to 10.5%, and a BMI of 18.5 to 35 kg/m$^2$<br>*Intervention*<br>Empagliflozin 2.5 mg P.O. daily<br>Empagliflozin 10 mg P.O. daily<br>Empagliflozin 25 mg P.O. daily<br>*Comparison*<br>Placebo<br>*Duration*<br>4 weeks | Change in A1C from baseline to 4 weeks (2° outcome) — *mean, %*<br>Empagliflozin 2.5 mg: −0.53[a]<br>Empagliflozin 10 mg: −0.54[a]<br>Empagliflozin 25 mg: −0.67[a]<br>Placebo:−0.18<br>Change in weekly total insulin dose from baseline to 4 weeks (2° outcome) — *mean, units/kg*<br>Empagliflozin 2.5 mg: −0.08[a]<br>Empagliflozin 10 mg: −0.10[a]<br>Empagliflozin 25 mg: −0.09[a]<br>Placebo: −0.01<br>Change in weight from baseline to 4 weeks — *mean ± SE, kg*<br>Empagliflozin 2.5 mg: −1.4 ± 0.3[a]<br>Empagliflozin 10 mg: −1.6 ± 0.3[a]<br>Empagliflozin 25 mg: −1.7 ± 0.3[a]<br>Placebo: +0.2 ± 0.3 |

Δ = difference versus placebo; A1C = glycated hemoglobin; BMI = body mass index; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; IU = international unit; P.O. = orally; SE = standard error; SGLT-2 = sodium glucose cotransporter-2; T1D = type 1 diabetes.

[a]*P* value < 0.05 when compared with placebo.

Overall, use of SGLT-2 inhibitors as adjunctive therapy to insulin appears to reduce A1C,[13,20,25] total daily insulin dose,[13,24,25] and weight compared with placebo.[13,20,24,25] Where statistical comparison was available, SGLT-2 inhibitors reduced A1C by approximately 0.3% to 0.7%.[13,20,25] Available data indicate a small numerical decrease in FPG when SGLT-2 inhibitors were added to insulin regimens.[13,20,25,54] SGLT-2 inhibitors reduced total daily insulin dose by approximately three to 20 units compared with placebo.[13,20,24,25] Weight loss ranged between 0.3 and 4.4 kg.[13,20,25,54] This reduction in weight was seen among populations with a normal[24] and high mean baseline BMI.[13,20] A recent meta-analysis of trials of SGLT-2 inhibitors reported similar results. This meta-analysis combined four randomized clinical trials and found that the use of SGLT-2 inhibitors as oral adjunct therapy to insulin in patients with T1D results in reductions in:

- FPG (mean difference [MD] = −0.69 mmol/L [95% CI, −1.32 to −0.07])
- A1C (MD = −0.37% [95% CI, −0.54 to −0.20])
- body weight (MD = −2.54 kg [95% CI −3.48, −1.60])
- total daily insulin dose (MD = −6.22 units [95% CI, −8.04 to −4.40]).

Of note, these trials were generally of short duration (< 12 weeks) and had enrolled a small number of patients (< 100 patients). Also, one of the included trials (Sands et al. 2015[26]) evaluated sotagliflozin, which is not a true SGLT-2 inhibitor, as it also inhibits SGLT-1 receptors.[56]

Kuhadiya et al.[20] was the only study that assessed "triple therapy," which consisted of two T2D medications (dapagliflozin and liraglutide) in addition to insulin for treatment of T1D. Further studies would be needed to investigate whether there is a benefit of "triple therapy" for T1D patients.

Other measures that were reported in the SGLT-2 inhibitor studies were cardiovascular surrogate endpoints.[20,25] In the Kuhadiya et al. and Pieber et al. studies, the addition of an SGLT-2 inhibitor had a negative impact on lipid levels, causing increased total cholesterol and LDL cholesterol compared with placebo, but there was no difference in HDL cholesterol nor triglycerides compared with placebo.[20,25] No changes in systolic nor diastolic blood pressure were seen with the use of an SGLT-2 inhibitor compared with the use of placebo.[20,25]

### SGLT-1/SGLT-2 Inhibitors

## Table 5: Clinical Trials for SGLT-1/SGLT-2 Inhibitors

| Study | Study Design/Intervention/Comparator/Duration | Key Findings |
|---|---|---|
| Sotagliflozin<br>Sands et al. 2015[26]<br>N = 33 | *Design*<br>Phase II randomized, placebo-controlled, double-blind study<br>*Patent Population*<br>Patients aged 18 to 55 years with T1D who had been treated with either multiple daily insulin injections or CSII and had an FPG of ≤ 15 mmol/L and a A1C level of 7.0 to 9.0%<br>*Intervention*<br>400 mg sotagliflozin P.O. daily<br>*Comparison*<br>Placebo<br>*Duration*<br>29 days | Change in total daily insulin bolus dose from baseline assessed at days 3 to 27 (1° outcome) — *presumed mean, %*<br>Sotagliflozin: −32.0[a]<br>Placebo: −6.4<br>Change in total daily insulin dose from baseline assessed at days 3-27 —*presumed mean, %*<br>Sotagliflozin: −15.3[a]<br>Placebo: −0.7<br>Change in A1C at from baseline to day 29 — *presumed mean, %*<br>Sotagliflozin: −0.55[a]<br>Placebo: −0.06<br>Change in body weight from baseline to day 29 — *mean, kg*<br>Sotagliflozin: −1.7[a]<br>Placebo: +0.5 |

| Study | Study Design/Intervention/Comparator/Duration | Key Findings |
|---|---|---|
| Sotagliflozin<br>Lexicon pharmaceuticals [33,57]<br>inTandem1<br>N = 793<br>*Unpublished* | *Design*<br>Phase III, double-blind, placebo-controlled study<br>*Patent Population*<br>T1D patients treated with multiple daily insulin injections or CSII who had a A1C level of 7.0 to 11.0%<br>*Intervention*<br>Sotagliflozin 200 mg P.O. daily<br>Sotagliflozin 400 mg P.O. daily<br>Comparison<br>Placebo<br>*Duration*<br>24 weeks | Change in A1C from baseline to 24 weeks (1° outcome) — *mean, %*<br>Sotagliflozin 200 mg : −0.43 Δ=0.36%[b]<br>Sotagliflozin 400 mg : −0.49 Δ=0.41%[b]<br>Placebo : −0.08 |

Δ = difference; A1C = glycated hemoglobin; CSII = continuous subcutaneous insulin infusion; FPG = fasting plasma glucose; P.O. = orally; SGLT-1 = sodium glucose transporter-1; SGLT-2 = sodium glucose cotransporter-2; T1D = type 1 diabetes.

[a]*P* value < 0.05 compared with placebo.

[b]*P* < 0.001 compared with placebo.

Compared with the other antihyperglycemic agents, there are still only very few studies investigating the use of SGLT-1/SGLT-2 inhibitors in T1D (Table 5). These studies tested sotagliflozin.[26,33] Available data suggest that the addition of sotagliflozin to insulin reduces A1C by approximately 0.4% to 0.5%, compared with insulin alone.[26,33] In the single study that reported on insulin use and weight change, the addition of sotagliflozin to insulin appears to reduce total daily insulin dose and weight (by approximately 2 kg) compared with insulin alone[26] In interpreting the glycemic results of the inTandem1 trial (Table 5), it should be noted that there was a six-week insulin optimization phase. Also, recently released results from the inTandem1 trial include a statistically significant reduction in body weight in both the 200 mg and 400 mg sotagliflozin arms (data not reported). A positive impact on blood pressure and no increase in severe hypoglycemic events were also seen (data not reported).[57]

At this time, in addition to inTandem1, there are two other phase III trials of sotagliflozin in T1D patients: inTandem2 and inTandem3. While inTandem1 recruited patients in North America, patients in the inTandem2 trial were recruited from Europe and Israel. The inTandem3 trial is a global study of 1,400 patients comparing the addition of sotagliflozin 400 mg once daily, or placebo, to insulin therapy. There was no insulin optimization prior to randomization. Detailed results of these trials have not been released yet.[57]

### *Overall Findings*

In summary, GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, and the SGLT-1/SGLT-2 inhibitor are currently experimental drugs being tested for adjunctive therapy in T1D patients. Available data suggest that these drugs may reduce A1C by 0.1% to 0.6% and the total daily insulin dose by 1 to 25 units/day, although combining insulin with some of the DDP-4 inhibitors or GLP-1 agonists did not appear to provide a beneficial effect in some studies. Overall, the reduction in total daily insulin dose suggests that these antidiabetic agents may have an insulin-sparing effect. All of these drugs, with the exception of DPP-4 inhibitors, also appear to reduce weight by 0.3 kg to 6.8 kg, depending on the drug and dose used. Notably, these results are based on preliminary data, and further studies are warranted to determine the true effect of these drugs. As such, the place of these drugs in the management of T1D is still undefined.

### *General Limitations*

The following is a short description of the key limitations of the trials reviewed in this report (as an in-depth critical appraisal of these studies is beyond its scope). The major limitations were the short duration and small sample size of several studies. The short study duration limits the ability to assess the long-term effect of these agents on efficacy outcomes. For example, the maximum effect of an antidiabetic drug on A1C takes 12 weeks to achieve, and many studies were less than 12 weeks in duration.[52] However, some of the included trials did have longer durations and recruited higher numbers of patients, including ADJUNCT ONE, which had a duration of 52 weeks and recruited more than 1,300 patients (Table 2). Another consideration is that unbalanced groups could have occurred because of the small sample sizes.[24,25] It was also noted that the pharmaceutical industry funded a number of these studies.

As a result of the presence of heterogeneity between studies in terms of type of drug, dosage regimen, population studied, and

insulin adjustments, the ranges of effect estimated in this report are associated with a certain level of uncertainty. In addition, studies of different designs may have been used to estimate the effect of some drugs; such approach may add to the uncertainty related to the interpretation of the results. Notably, no statistical pooling of study results was performed in this report; such an approach was beyond the scope of this project, which essentially aimed to describe the emerging use of newer drugs for T2D to treat patients with T1D. There are a few pooled results included in the Evidence section, but they were reported by authors of included meta-analyses.

It is also uncertain whether the 1kg to 5 kg (or approximately 1% to 7% based on a 70 kg person) weight loss associated with GLP-1 agonists, SGLT-2 inhibitors, and SGLT-1/SGLT-2 inhibitors will have an impact on cardiovascular outcomes. Diabetes Canada reports that weight loss of 5% to 10% of initial body weight can improve insulin sensitivity, glycemic control, high blood pressure, and dyslipidemia.[38] However, this finding was mainly based on an interim analysis of a study (Look AHEAD) that was eventually stopped early at the end of 10 years due to the fact that no significant difference in cardiovascular morbidity and mortality was measured, despite a mean weight loss of 6%.[58]

There are also limitations in the applicability of these results to the general T1D population due to the studies' extensive exclusion criteria. For example, patients with a previous history of pancreatic disease, gastroparesis, renal disease, liver disease, cancer, seizures, hypoglycemia unawareness, or major illness were excluded. Pregnant and breastfeeding patients were also excluded.[19-21,24] Appraising the exclusion criteria further is beyond the scope of this horizon scan.

## Adverse Events

The addition of GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, and the SGLT-1/SGLT-2 inhibitor to insulin is associated with an incidence of hypoglycemia that is similar to incidence reported with insulin monotherapy.

The occurrence of any hypoglycemic events was, as expected, generally very common in both the treatment arm and placebo arm in the GLP-1 agonist (50% to 90%)[17,21,41] and SGLT-2 inhibitor studies (60% to 95%).[13,24] Studies indicate that the risk of severe hypoglycemia is lower, ranging from 2% to 9%[17,41] for GLP-1 agonists and 0% to 7% for SGLT-2 inhibitors, when these drugs are used as adjuvant therapy in patients with T1D.[13,20,24]

Studies reported a 0% to 15% rate of serious adverse events and adverse events leading to premature discontinuation of therapy with GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, and the SGLT-1/SGLT-2 inhibitor.[17,18,26,33,35,52] In ADJUNCT TWO, there were two acute coronary syndromes and one cerebrovascular event in the liraglutide groups compared with one acute coronary syndrome in the placebo group.[41] Authors did not comment on whether these events were treatment related.[41] Additionally, there was one malignant neoplasm and one thyroid event requiring thyroidectomy in the liraglutide 1.8 mg group.[41] In the study by Garg et al., there were two withdrawals from the sitagliptin treatment group; one patient developed a skin rash, and another patient developed esophageal cancer, which investigators determined was not likely to be drug related.[22] Among the SGLT-2 studies, Henry et al. reported one case of gastroparesis in a patient receiving dapagliflozin, but investigators reported it was not related to treatment.[24] Given that the number of serious adverse events reported was low, it is difficult to draw firm conclusions at this time.

Studies investigating GLP-1 agonists, SGLT-2 inhibitors, and the SGLT-1/SGLT-2 inhibitor reported diabetic ketoacidosis (DKA) in treatment groups, whereas studies investigating DPP-4 inhibitors did not report any DKA. There was a numerically greater occurrence of DKA in patients treated with a GLP-1 agonist compared with those on a placebo. Investigators in the ADJUNCT ONE trial theorized that the higher incidence of DKA was linked to the higher incidence of nausea associated with liraglutide treatment.[17] In the Kuhadiya et al. study, two patients in the dapagliflozin group experienced DKA, one of which had euglycemic DKA.[20] In the canagliflozin study by Henry et al., there were 12 serious DKA cases in patients that received canagliflozin compared with none in the placebo group.[13] In the inTandem1 trial, an increase in the risk of developing DKA was also observed in patients using sotagliflozin; this increase appears to have been dose-dependent, i.e., 0.0% (placebo), 1.1% (sotagliflozin 200 mg), and 3.1% (sotagliflozin 400 mg). These adverse events were also more frequent in patients using insulin pumps compared with patients using multiple daily injections.[57] An increase in the risk of DKA was also reported in the meta-analysis by Chen et al.[56] In general, the investigators of included trials reported that the majority of patients with DKA had precipitating factors that likely contributed to the development of DKA (e.g., infection, inadequate carbohydrate intake, pump failure, or cessation of insulin therapy).[13,20,26,56] One study reported similar occurrences of DKA among T1D patients on insulin using different doses of dapagliflozin or placebo as adjuvant therapy, i.e., 1% (4/277), 2% (5/296) and 1% (3/260) in patients in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively.[55]

GLP-1 agonists and the SGLT-1/SGLT-2 inhibitor had higher incidences of gastrointestinal (GI) adverse events compared with placebo. Nausea was the most frequent GI adverse event for both

GLP-1 agonists and the SGLT-1/SGT2 inhibitor. In most cases, this adverse event was transient, but a few patients had to reduce their dose of liraglutide,[14,17-19,41] and two patients withdrew.[19,43] In two of these studies, the rate of GI adverse events with GLP-1 agonists was determined to be dose-dependent.[17,41] In the recent meta-analysis by Panta et al., the use of liraglutide for 12 weeks in 212 patients with T1D was associated with a significant increase in nausea when compared with placebo (odds ratio 6.55, 95% CI, 2.32 to 18.48). However, there was no increase in the risk of vomiting (odds ratio 1.67, 95%, CI, 0.34 to 8.13).[49,50] There was only one study that reported on incidence of pancreatitis, and it reported one case, which occurred in the liraglutide 0.6 mg group.[17]

Other adverse events that were reported with SGLT-2 inhibitors were urinary infection, genital infection, headache, and back pain.[13,25] Henry et al. reported a higher incidence of female genital mycotic infections with higher doses of canagliflozin (21.2%) compared with lower doses of canagliflozin (4.2%) and placebo (5.6%).[13] Pieber et al. reported one urinary tract infection and a low rate of headache and back pain in the empagliflozin groups. In contrast to the SGLT-2 inhibitor studies, there were no genitourinary infections reported with sotagliflozin treatment.[26]

### *Overall Findings*

Most of the adverse events that occurred with the use of GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors in T1D patients have also been reported in studies with T2D patients, including hypoglycemia, nausea, and genitourinary infections. Of particular note, in May 2016, Health Canada warned that DKA had been reported with use of SGLT-2 inhibitors in T1D and T2D patients.[59] It was reported that a large portion of the DKA cases occurred in T1D patients, and some of the patients had an atypical presentation where there were only moderately increased blood glucose levels.[59] Heath Canada reported that T1D and a sudden insulin dose reduction may predispose a patient to ketoacidosis.[59] This risk needs to be assessed further in studies on T1D patients.

### *General Limitations*

The safety assessment of these drugs is limited by the studies' short duration and small sample sizes. Some studies did not perform statistical testing on adverse events. It is also difficult to assess the rates of hypoglycemia and serious adverse events, as some studies did not report on these measures or did not provide definitions for these parameters. Many of these studies were funded by industry.

## Administration and Cost

### *Administration*

DPP-4 inhibitors, SGLT-2 inhibitors, and SGLT-1/SGLT-2 inhibitors are administered orally. All of the available agents in Canada are administered once daily, so they would be convenient for patients.

GLP-1 agonists are administered subcutaneously once to twice daily. T1D patients would be familiar with the subcutaneous route of administration, as insulin is delivered by the same route; thus, minimal teaching would be required. T1D patients may also already have the supplies to administer subcutaneous medications (e.g., needles and sharps container). However, some patients may be resistant to the idea of administering additional injections compared with taking an oral drug in addition to their insulin injections. The development of fixed-ratio combination insulin and GLP-1 agonist products, such as insulin degludec/liraglutide (IDegLira), could offer an alternative in these situations, although current clinical development is for patients with T2D.[60]

### *Cost*

The newer medications for T2D are relatively expensive. The daily price of GLP-1 agonists and DPP-4 inhibitors available in Canada can range from $4.59 to $7.34 and $2.84 to $2.95, respectively.[61-63] The daily price of an SGLT-2 inhibitor is approximately $2.62.[63,64] The price of an SGLT-1/SGLT-2 inhibitor is not available, as it has not yet been approved for sale in any country. By comparison, the cost of insulin ranges from $0.03 to $0.07/unit.[65] Overall, it may be projected that adjunctive therapy to insulin in T1D could result in a significant budget impact for patients and payers. A formal pharmacoeconomic analysis would be needed to determine whether adopting adjunctive therapy would provide good value for the health system and patients.

## Concurrent Developments

There are multiple ongoing studies listed on ClinicalTrials.gov that are investigating the use of GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors for T1D. For example, dapagliflozin is being investigated in two large phase III global studies as adjunctive treatment in patients with T1D: DEPICT 1 (NCT02268214)[66] and DEPICT 2 (NCT02460978).[67] In addition, NCT02582814 is a recently completed phase III trial investigating the safety and efficacy of dapagliflozin therapy in combination with insulin in Japanese patients.[68] Another example is NCT02516657,[69] a phase III trial that will study the effect of liraglutide in adolescents with T1D that is currently recruiting participants.

As previously mentioned, Lexicon Pharmaceuticals is also conducting two other phase III clinical trials on sotagliflozin for T1D diabetes (inTandem2 and inTandem3).[33] The inTandem3 trial differs from the inTandem2 trial; inTandem2 has an insulin optimization period prior to randomization, whereas there is no stabilization period inTandem3.[33] Also, inTandem1 recruited patients in North America, whereas inTandem3 is a global trial.[57] Top-line results for both inTandem2[33] and inTandem3[70] trials were recently announced by the manufacturer.

DPP-4 inhibitors have also been studied for use with a proton-pump inhibitor. Griffin et al. conducted a study titled REPAIR-T1D that investigated the use of sitagliptin and lansoprazole in T1D patients based on the theory that this combination would preserve beta-cell function in patients with recent-onset T1D.[71] Clinical outcome data were not presented.[71]

These newer T2D agents have also been studied in other populations. For example, DPP-4 inhibitors have been studied in patients with recent-onset latent autoimmune diabetes[53] and patients with new-onset diabetes after renal transplantation.[72,73] GLP-1 agonists have been studied in patients who have received islet transplantation.[74,75] Studies have also investigated daclizumab in addition to exenatide plus insulin in T1D patients.[48]

## Rate of Technology Diffusion

It is expected that the use of GLP-1 agonists, DPP-4 inhibitors, SGLT-2 inhibitors, and SGLT-1/SGLT-2 inhibitors in T1D patients will likely be limited to patients who are gaining weight and have poor glycemic control with insulin alone. Endocrinologists would be expected to be the main prescribers of these adjuvant therapies. The rate of technology diffusion will also be influenced by long-term safety and efficacy data. Moreover, price and cost-effectiveness are other factors that will affect the diffusion of this technology to T1D patients. Lastly, none of these drugs is currently approved in Canada for the adjuvant treatment of patients with T1D.

## Implementation Issues

A current barrier to the uptake of these newer drugs is the lack of information on how to integrate them into practice. Data are lacking on how to optimally adjust a patient's insulin dose when a GLP-1 agonist, DPP-4 inhibitor, SGLT-2 inhibitor, or an SGLT-1/SGLT-2 inhibitor is initiated. Furthermore, comparative studies are needed to determine which drug to try first as adjunctive therapy and at which dose. Determining how to adjust the doses of these newer drugs in patients with liver or renal impairment or in patients taking medications that interact with them will also be important.

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