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Review

Fixed-Dose and Fixed-Ratio Combination Therapies in Type 2 Diabetes

Robert Schlosser MD, FRCPC *

LMC Diabetes & Endocrinology-Vaughan, Thornhill, Ontario, Canada

Key Messages

- Early combination antihyperglycemic medications with complementary mechanisms of action are recommended by clinical practice guidelines.
- Oral fixed-dose combinations with metformin are frequently prescribed to reduce pill burden.
- Newer fixed-ratio insulin + GLP1 receptor agonist combinations are highly efficacious options for patients requiring injectable therapy.

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ABSTRACT

The progressive natural history underlying type 2 diabetes often necessitates the use of multiple antihyperglycemic medications to achieve therapeutic goals and targets. The associated complexity of these regimens presents significant challenges to both physicians and patients. Fixed-dose oral and fixed-ratio injectable combination agents offer significant potential to simplify and consolidate therapy and lessen barriers to adherence.

RÉSUMÉ

L'évolution naturelle du diabète de type 2 exige souvent l'utilisation de nombreux antihyperglycémiants pour atteindre les objectifs thérapeutiques et les valeurs cibles. La complexité de ces traitements est un enjeu important auquel font face les médecins et les patients. Le traitement combiné par voie orale à dose fixe et par voie injectable en proportion fixe a un potentiel considérable pour simplifier et consolider le traitement, et diminuer les obstacles à l'observance.

Introduction

Despite numerous recent therapeutic advances in the management of type 2 diabetes, indicators of metabolic control remain essentially unchanged with over half of the diabetic population being at >7% of the glycated hemoglobin (A1C) target (1). Multiple contributing factors include the progressive natural history of the disease, physician-related therapeutic inertia, patient challenges in adherence and complexity of treatments, fear of adverse side effects and systemic issues related to cost and inadequate public/private drug coverage.

Diabetes Canada clinical practice guidelines (2,3) continue to recommend metformin as the drug of first choice plus consideration of early combination antihyperglycemic agent (AHA) medication strategies when A1C is >1.5% over the patient's individualized target. Although the recent consensus report by the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) notes there is little evidence that this approach is superior to sequential addition of medications (4), real-world evidence indicates a significant delay in oral agent treatment intensification of almost 3 years at an A1C of 7% to 7.5% and 1.6 years at an A1C of >8% (5). Time to insulin initiation is country dependent but is often >7 years (6).

Fixed-dose and fixed-ratio combination therapies with complementary mechanisms of action provide the opportunity to achieve earlier and more sustainable glycemic control with increased patient adherence and reduced side-effect profiles. There is also the potential to reduce disease progression and vascular

* Address for correspondence: Robert Schlosser MD, FRCPC, LMC Diabetes & Endocrinology-Vaughan, 5-1600 Steeles Avenue West, Thornhill, Ontario L4K 4M2, Canada.
E-mail address: robert.schlosser@lmc.ca

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Table 1
Fixed dose and fixed ratio combinations approved in Canada

AHA class	Components	Brand name	Doses (mg)
DPP4i–metformin			
	Aloglipin–metformin	Kazano	12.5+500/850/1,000
	Linagliptin–metformin	Jentadueto	2.5+500/850/1,000
	Saxagliptin–metformin	Komboglyze	2.5+500/850/1,000
	Sitagliptin–metformin	Janumet	50+500/850/1,000, 50+500/1,000 XR, 100+1,000 XR
SGLT2i–metformin			
	Canagliflozin–metformin	Invokamet	50+500/850/1,000, 150+500/850/1,000
	Dapagliflozin–metformin	Xigduo	5+850/1,000
	Empagliflozin–metformin	Synjardy	5+500/850/1,000, 12.5+500/850/1,000
	Ertugliflozin–metformin	Segluromet	2.5+500/1,000, 7.5+500/1,000
TZD–metformin	Rosiglitazone–metformin	Avandamet	2+500/1,000, 4+500/1,000
TZD–sulfonylurea	Rosiglitazone–glimepiride	Avandaryl	4+1/2/4
DPP4i–SGLT2i			
	Linagliptin–empagliflozin	Glyxambi	5+10/25
	Saxagliptin–dapagliflozin	Qtern	5+5/10
	Sitagliptin–ertugliflozin	Steglujan	100+5/15
Insulin–GLP-1 RA			
	iDegludec–liraglutide	Xultophy	16 U per 0.6 mg to 50 U per 1.8 mg
	iGlargine–lixisenatide	Soliqua	15 U per 5 μg to 60 U per 20 μg

AHA, antihyperglycemic agent; *DPP4i*, dipeptidyl peptidase 4 inhibitor; *GLP-1 RA*, glucagon-like peptide-1 receptor agonist; *SGLT2i*, sodium glucose transporter-2 inhibitor; *TZD*, thiazolidinedione; *XR*, extended release.

complication risk as well as possible cost savings compared with the individual medication components. Table 1 lists the combination medications approved in Canada. The most widely prescribed are dipeptidyl peptidase 4 (DPP4)–metformin fixed-dose combinations (FDCs) followed by sodium glucose transporter-2 (SGLT2)–metformin FDCs. The thiazolidinedione (TZD) combinations are listed for completeness but rarely prescribed, and the approved DPP4–SGLT2 combinations have thus far not been marketed. Two new insulin–glucagon-like peptide-1 receptor agonist (GLP-1 RA) fixed-ratio combinations (FRCs) received a notice of compliance in 2018, representing a novel approach to injectable antihyperglycemic therapy.

Multiple interrelated and overlapping pathophysiologies contribute to hyperglycemia in type 2 diabetes. This concept was coined the “ominous octet” in 2008 by Dr. Ralph Defronzo (7). This elegant model emphasizes the heterogeneity of this complex disease (as different mechanisms may predominate in individual patients) as well as the rationale and frequent need for combination therapies with complementary mechanisms of action. Indeed, each of these 8 systems are targeted by current AHA medication classes. Specifically, DPP4 inhibitor (DPP4i) and GLP-1 RA incretins effect glucose-dependent alpha and beta islet-cell function with GLP-1 RAs also delaying gastric emptying and exhibiting central appetite-suppressing and satiety-enhancing effects. Insulin secretagogues (and exogenous insulin replacement) nonspecifically increase circulating insulin action. Metformin primarily reduces hepatic glucose production with secondary effects on peripheral insulin resistance in muscle and fat (along with TZD sensitizers). The newest AHA class, the SGLT2 inhibitors, fills the gap by reducing renal glucose reabsorption, which is insulin independent.

The Diabetes Canada guidelines (3) recommend minimizing hypoglycemia and avoiding weight gain as priorities after considering the presence or absence of established cardiovascular disease. Therefore, incretin medications and SGLT2 inhibitors are favoured over sulfonylureas, TZDs and insulin. The ADA/EASD consensus (4) further states that GLP-1 RAs are preferred over insulin as the first injectable therapy in the absence of extreme hyperglycemia with symptoms, a suspicion of underlying latent autoimmune type 1 diabetes of adulthood or special situations requiring short-term insulin such as preconception and pregnancy.

Initiation of metformin FDC therapies has been studied primarily in drug-naive patients with high baseline A1C (mean, 8.8%). Greater attainment of A1C targets was seen with initial sitagliptin/metformin (8) and canagliflozin/metformin (9) compared with metformin alone in the respective studies. No excess hypoglycemia was noted. Greater weight loss occurred with the SGLT2-inhibitor–based combination and side effects were as expected with each agent, although some studies suggest decreased gastrointestinal symptoms, such as nausea and diarrhea, with the FDC.

Addition of DPP4–SGLT2-inhibitor FDCs to background metformin has similarly been evaluated in 2 separate studies reported in the same issue of *Diabetes Care* (March 2015). From a mean baseline A1C of 8.9%, the mean reduction with saxagliptin–dapagliflozin was 1.5%, significantly higher than the 1.2% reduction with dapagliflozin and 0.9% reduction with saxagliptin alone (10). A1C target was achieved in 41% of FDC patients (compared with 18% to 22% with only 1 additional AHA medication). Starting from a lower baseline A1C of 7.9% to 8.0%, the FDC linagliptin–empagliflozin achieved A1C target in 57.8% to 61.8% of patients compared with 28% to 36% with either agent alone (11). Efficacy was maintained at 52 weeks with no increased hypoglycemia risk.

A meta-analysis involving >70,000 patients in 10 observational studies showed a significant 0.53% A1C reduction with FDCs compared with coadministered dual therapies associated with improved adherence, as measured by a 5.0% to 8.6% increase in medication possession ratio (12). More recently, the retrospective GIFT study reported a 0.3% to 0.4% A1C reduction after a switch from separate metformin and DPP4 inhibitor to an FDC (13). The greatest improvement was seen in patients with the highest pill burden (≥10 pills/day), reinforcing the potential benefits of consolidating AHA therapies. This is consistent with the 2003 World Health Organization report (14) citing numbers of medications (>5) and doses (>12) as major predictors of poor adherence, especially in elderly individuals with multiple comorbidities.

In a review of 17 studies (15), adherence was 10% to 13% higher with the FDC in patients starting combination therapy. In 4 of 5 publications, FDC was associated with greater patient satisfaction according to the Diabetes Treatment Satisfaction Questionnaire. Limited economic analyses in 2 studies trended toward reduced health-care utilization costs. In a large, retrospective cohort study of >23,000 patients (16), FDCs were associated with 28% higher odds of adherence (odds ratio, 1.28; 95% confidence interval, 1.20 to 1.36; $p<0.0001$) and an 8.4% reduction in diabetes-related costs.

In addition to pill burden and cost concerns, tolerability and perceived adverse effects present significant barriers to optimal adherence and metabolic control. Excluding hypoglycemia related to sulfonylureas and insulins, gastrointestinal issues are the most common cause of medication nonadherence and lower scores on

health-related quality of life (17). Lower incidence of abdominal pain and diarrhea side effects have been reported in prospective studies with the sitagliptin–metformin FDC (8) compared with metformin alone.

Fixed-Ratio Combinations: A New Therapeutic Option

Basal insulin initiation is an excellent option for many patients with inadequate fasting glucose control. Newer basal analogues have the advantages of a flatter pharmacodynamic profile, longer duration and reduced glycemic variability. Risks of hypoglycemia and weight gain are significantly reduced and can often be further mitigated by combining with "insulin-sparing" medications such as metformin, incretins and SGLT2 inhibitors, all of which can improve nonfasting (postprandial) glucose control. More specifically, utilizing basal insulin with a GLP-1 RA in the same injection device can simplify titration of both components (potentially requiring lower doses of each), thus improving patient adherence.

Insulin degludec and liraglutide

The FRC of the insulin degludec 100 U/mL and the GLP-1 RA liraglutide 3.6 mg/mL (Xultophy, Novo Nordisk, Bagsværd, Denmark) has been evaluated within the DUAL clinical trial program. Populations included patients uncontrolled on background oral antihyperglycemic medications (DUAL 1 [18,19], 4 [20], 6 [21] and 9 [22]), basal insulins (DUAL 2 [23], 5 [24], 7 [25]) or a GLP-1 RA (DUAL 3 [26]). All trials achieved significant A1C reductions relative to comparators (baseline, 7.8% to 8.7%; final, 6.0% to 6.9%), with weight loss and less hypoglycemia in trials against an active insulin titration arm (Figure 1).

Canadian indications, including treatment of adults with type 2 diabetes mellitus on basal insulin (<50 units/day, based on DUAL 2 and 5) or liraglutide (≤1.8 mg/day, based on DUAL 3), do not provide adequate glycemic control in combination with metformin with/without a sulfonylurea (27). Although approved in the European Union as a first injection option in patients failing oral antihyperglycemic medication, there is currently no such indication in the Canadian product monograph.

The recommended starting dose is the equivalent of 16 units of insulin degludec (0.58 mg liraglutide) in a prefilled 3.0-mg FlexTouch (Novo Nordisk) pen device, given once daily at any time of the day. Titration is based on fasting glucose target range (increase 2 units if above, reduce 2 units if below range) every 3 to 4 days (27). However, the DUAL 6 trial demonstrated equivalent efficacy with once-weekly titration (17). The maximum insulin dose is 50 units of degludec, which equals the maximal liraglutide (Victoza, Novo Nordisk) dose of 1.8 mg/day. No new safety issues have been identified; however, the incidence of GLP-1 RA gastrointestinal side effects (particularly nausea) is reduced due to slower dose escalation compared with standard GLP-1 RA titration regimens.

In a retrospective, real-world European experience study (EXTRA) (28), 71% of patients were on basal insulin (with/without prandial insulin or separate GLP-1 RA injections), 10% on GLP-1 RA without insulin and 19% on oral antihyperglycemic agents. The largest A1C change from baseline was seen in the insulin-naive groups (−1.6% for oral-agent group, −1.0% for GLP-1 RA baseline, −0.6% to −0.9% for insulin-experienced groups), but final A1C was similar at 7.3% to 7.6% (from a baseline of 8.3% to 8.9%), with an average insulin dose range of 26 to 37 units/day. Hypoglycemia was infrequent, but decreased from 0.28 to 0.06 event/patient-year after insulin degludec and liraglutide (iDegLira) initiation. There was no significant weight change in any group, except for a 2.4-kg weight loss from baseline basal-bolus multiple-dose insulins.

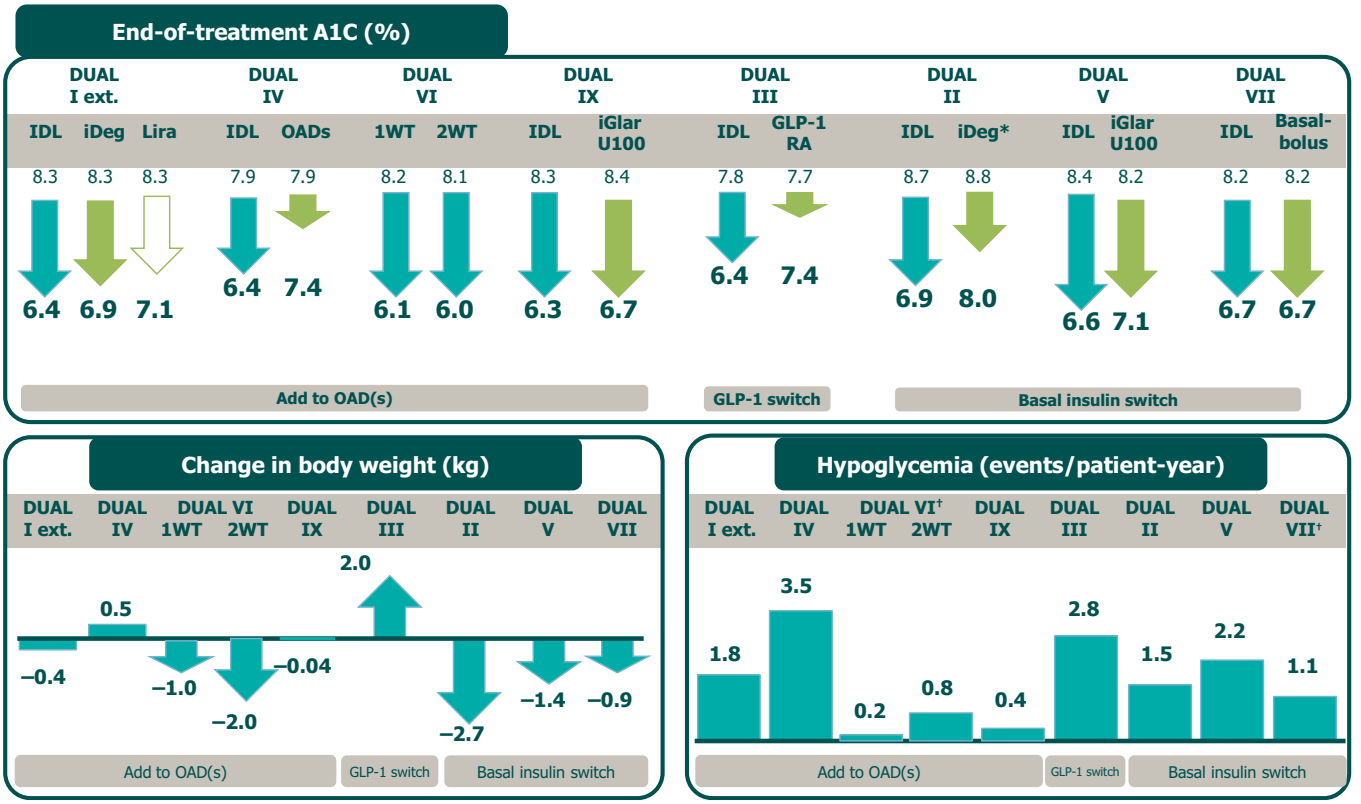

Figure 1. DUAL Trials programme: Key results (18–26). *A1C*, glycated hemoglobin; *GLP-1*, glucagon-like peptide-1 receptor agonist; *IDL*, insulin degludec and liraglutide; *iDeg*, insulin degludec; *iGlar*, insulin glargine; *Lira*, liraglutide; *OAD*, oral antidiabetic; *1WT*, once-weekly titration; *2WT*, twice-weekly titration.

Insulin glargine and lixisenatide

The FRC of insulin glargine 100 U/mL (U100) and the GLP-1 RA lixisenatide 33 μg/mL (Soliqua, Sanofi-Aventis, Paris, France) has been evaluated within the LixiLan clinical trial program.

The LixiLan-O trial enrolled patients inadequately controlled on 1 or 2 oral agents, including metformin (baseline A1C 8.2%) (29). The primary A1C outcome was superior in favour of the combination against lixisenatide (6.5% vs 7.3%) and against insulin glargine U100 (6.5% vs 6.8%) titrated up to a maximum of 60 units/day (Figure 2). Body weight was essentially unchanged in the LixiLan arm, increased in the insulin arm (+1.1 kg) and reduced in the GLP-1 RA arm (−2.3 kg). Documented hypoglycemia (<3.9 mmol/L) was similar in the insulin glargine and lixisenatide (iGlarLixi) and glargine groups, and much lower in the lixisenatide group, as expected. Average daily insulin dose was 40 units in both the combination and insulin-only arms. Gastrointestinal side effects were more common in patients receiving a GLP-1 RA, with less reported nausea (9.6% vs 24%) with the combination.

In the LixiLan-L trial, patients with type 2 diabetes on stable background basal insulin therapy (15 to 40 units/day) and inadequate A1C control (7.5% to 10%) were randomized to iGlarLixi vs glargine U100 (up to maximum 60 units/day) (30). From the baseline A1C of 8.1% at randomization, the combination group was superior to the basal insulin group (6.9% vs 7.5%), with a 1.4-kg weight difference (Figure 2). Hypoglycemia frequency was similar in both groups (40% vs 42.5% of patients) as was final insulin dose (47 units). As expected, nausea was more common with the combination (10.4%), but the discontinuation rate was low (1.1%).

Indications in Canada are for treatment of adults with type 2 diabetes mellitus inadequately controlled on basal insulin (<60 units/day) alone or in combination with metformin (31), based on the LixiLan-L trial. There is currently no indication for use as the first injection option in patients failing oral antihyperglycemic medications.

The recommended starting dose depends on the patient's previous basal insulin dose: 15 units (with 5 μg lixisenatide) if basal dose <30 units/day and 30 units (with 10 μg lixisenatide) if basal dose is 30 to 60 units/day. It is available in a prefilled 3.0-mg SoloSTAR pen device (Sanofi-Aventis, Paris, France), given once daily within 1 hour prior to the first meal. Titration is by 2 to 4 units per week until the patient's target fasting glucose is achieved. The maximum insulin dose is 60 units of glargine, which results in a maximum lixisenatide dose of 20 μg/day (31).

It should be noted that the starting dose of an FRC is determined by the recommended initiation dose of the GLP-1 RA component (0.6 mg/day liraglutide, 5 or 10 μg/day lixisenatide) to reduce the incidence of adverse gastrointestinal side effects, particularly nausea. Although this usually represents a reduction from the patient's previous baseline insulin dose (to 16 units iDegLira and to 15 or 30 units of iGlarLixi), glycemic control did not decline significantly in the various studies due to the introduction of GLP-1 RA as well as prescribed titration of the FRC to fasting glucose targets. Titration is expected to be more rapidly achieved with the combination than with basal insulin alone.

A common question regarding FRCs is how to deal with patients who may require greater than the maximum allowable insulin dose (50 units for iDegLira, 60 units for iGlarLixi). Although there have been no randomized trials designed to answer this question, there are 3 general clinical approaches. First, the combination can be abandoned in favour of separate daily basal insulin and daily or weekly GLP-1 RA therapies to allow more flexibility. Alternatively, a separate injection of the same daily basal insulin can be added to the maximal FRC (although this would be considered off-label use). Finally, optimization of other therapies, including diet, lifestyle and other noninsulin antihyperglycemic agents, can be attempted if possible.

Another concern is dealing with a situation where one may wish to adjust or stop one of the combination components but not the other. Although neither insulins or GLP-1 RA medications are part

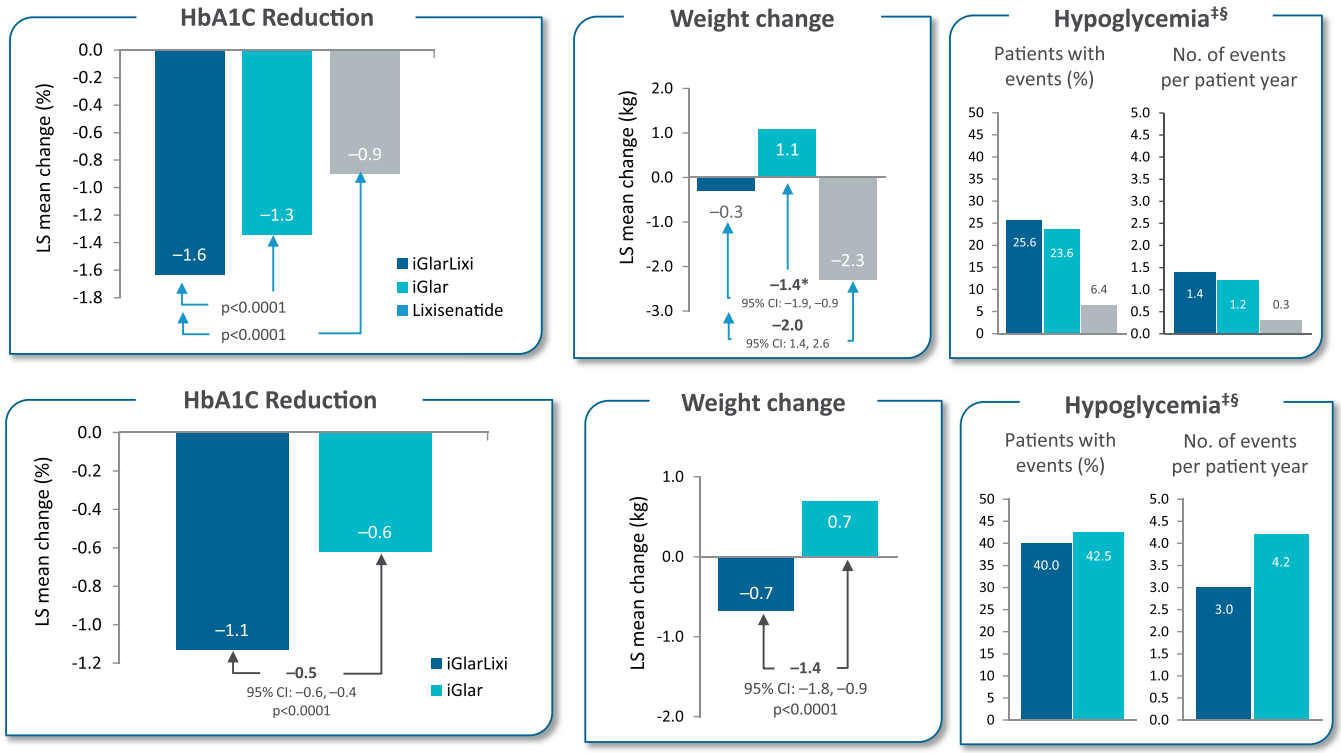

Figure 2. LixiLan-O and -L Trials: Key results (29,30). *CI*, confidence interval; *HbA1C*, glycated hemoglobin; *iGlar*, insulin glargine; *Lixi*, lixisenatide; *LS*, least squares.

of the Diabetes Canada SADMANS sick-day recommendations, it is common for GLP-1 RA to be held in the case of a gastrointestinal illness and for individualized insulin adjustments with closer monitoring when oral intake is unpredictable. Therefore, it would seem prudent for patients to have a backup prescription for the corresponding basal insulin should the FRC need to be temporarily stopped.

There is minimal published evidence evaluating adherence, patient satisfaction and cost-effectiveness of FRCs. Given that these agents are relatively new, one would expect relevant data in the near future. As with oral FDC products, the cost of the combination is usually less (but certainly not greater) than the components if prescribed separately.

Conclusions

FDC and FRC antihyperglycemic products represent an important strategy with respect to introducing complementary therapies for type 2 diabetes in the effort to provide better glycemic control with a reduced side-effect profile. Regardless of the therapeutic advances available to our patients, simplified regimens with reduced pill and/or injection burdens should improve adherence and patient acceptance of the frequent need for combination therapies.

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R.S. is solely responsible for accuracy and content.

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