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THE CURRENT STATE OF FIXED-DOSE OADS

In this Issue...

The first-line challenge for clinicians treating most patients with type 2 diabetes, after counseling for lifestyle changes, is selection of an oral medication. Although the "step-wise" approach – initiating metformin, titrating up, and then adding a second oral agent – continues to be advocated in the guidance, newer research has found that initiating treatment with fixed-dose dual OAD therapy (aka "single pills") may be more beneficial in many patients. Fixed-dose OADs have also been shown to be valuable in up-titration, particularly in improving adherence in patients with multiple comorbidities and higher pill burdens.

In this issue, we review recent publications describing the use of fixed-dose OADs to individualize therapy and improve patient adherence.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Explain the rationale for fixed-dose combination OADs.
- Evaluate the efficacy, tolerability, cost and adherence related to fixed-dose combination OADs.
- Describe the benefits of fixed-dose combination OADs in tailoring type 2 diabetes therapy.

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COMMENTARY

Type 2 diabetes (T2DM) is a complex disease with multiple physiological causes, including impaired insulin secretion, peripheral and hepatic insulin resistance, and gut hormone dysfunction. Consequently, therapies have been developed to target each of these defects, which has increased the number of available treatment choices over the years for patients with T2DM. Despite this progress, attaining good glycemic control for the millions of adults with diabetes remains a challenge, in part due to the progressive failure of beta cells, insulin resistance, ineffective lifestyle, weight gain, and cost-related poor adherence to treatment. As a result, almost half of U.S. adults with diabetes do not meet the guidelines for diabetes care.[1] Therefore, improving the treatment of T2DM and its delivery to patients remains a high priority.

With an increasing number of medications available to treat T2DM, selecting the optimal therapeutic regimen for each patient is becoming less straightforward. Patients with T2DM often have other comorbidities requiring medication that contribute to overall pill burden. Fixed-dose combinations (FDC), also known as single-pill combinations, have the potential to reduce this pill burden and simplify the medication regimen, thus facilitating adherence and better glycemic control.

In addition, emerging evidence suggests that FDCs may work even more efficiently to lower blood glucose levels compared to their respective individual components ("syngergy"), while having similar safety and tolerability profiles, as well as possibly reducing health care costs. The FDCs for T2DM are largely divided into two groups: those containing metformin versus those that do not. Compared to metformin monotherapy, metformin-containing FDCs have been shown to lead to a greater reduction in hemoglobin HbA1C among users.

Metformin extended-release (XR) may offer additional benefits given once-daily dosing and milder gastrointestinal side effects. The article by Blonde et al specifically reviews the FDCs containing metformin XR, which include saxagliptin/metformin XR, pioglitazone/metformin XR, and sitagliptin/metformin XR. For patients who are unable to tolerate metformin, there are alternative FDCs, such as TZD plus sulfonylurea, TZD plus

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DPP4 inhibitor (eg, alogliptin and pioglitazone), SGLT2 inhibitor and DPP4 inhibitor (eg, dapagliflozin plus saxagliptin, empagliflozin plus linagliptin), SGLT2 inhibitor plus sulfonylurea, and SGLT2 inhibitor plus TZD.

For obvious reasons, FDCs have the potential to improve long-term patient adherence. In the article by Lokhandwala et al, patients in the FDC cohort reported a higher rate of adherence and lower rate of hypoglycemia than those prescribed multiple loose pills. Although prescription costs were higher in the FDC cohort, the all-cause monthly costs were lower in this group compared to the LDC group – suggesting possible economic benefits beyond monthly prescription costs.

One of the newest FDCs approved is empagliflozin/linagliptin, discussed in detail in the reviewed article by Kim et al. The efficacy of empagliflozin/linagliptin 10 mg/5 mg was shown to be better than the individual components while, surprisingly, empagliflozin/linagliptin 25 mg/5 mg did not show superior efficacy to its individual components. The side effects of empagliflozin/linagliptin were similar to the individual components and included urinary tract infection, upper respiratory tract infections, and nasopharyngitis.

The FDC of metformin and a DPP-4 inhibitor, commonly used in the US, is reviewed in detail in the article by Liu et al. In addition to convenience and tolerability, FDCs may be more efficient than their respective individual components due to additive effect of the combined medications, an effect that is explained through several mechanisms discussed in the article.

Altogether, FDCs may help improve glycemic control in patients with T2DM by facilitating adherence, reducing health care costs, and reducing side effects by avoiding maximum doses of each component medication. Consequently, there is a growing interest in their use as initial combination therapy. Indeed, a systematic review suggested a potential benefit of using a metformin-containing FDC as initial treatment compared to metformin monotherapy in patients with T2DM at varying HbA1C levels.[2] Many of the studies examining the role of FDCs were limited by the fact that they were largely sponsored by the pharmaceutical companies, and the effects of FDCs were often compared to those with monotherapy using one of the individual components.

While the FDCs appear promising in improving the treatment of T2DM, whether we need to shift the paradigm in the step-wise management of T2DM remains to be determined.

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FIXED-DOSE OADS TO INDIVIDUALIZE THERAPY IN PRIMARY CARE

Lavernia F, Adkins SE, Shubrook JH. Use of oral combination therapy for type 2 diabetes in primary care: Meeting individualized patient goals. *Postgrad Med*. 2015;127(8):808-817.

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In this article, the authors sought to provide primary care providers with an up-to-date review of the role of fixed-dose combination (FDC) therapies in improving the clinical care for patients with type 2 diabetes (T2DM). The challenges facing T2DM management in primary care include the progressive nature of T2DM, increasing complexity in managing diabetes due to an increasing number of available antihyperglycemic agents, and nonadherence related to cost, tolerability, and the complexity of daily treatment regimens.

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The authors discuss the limitations of the current stepwise approach to T2DM involving lifestyle modification, then additional monotherapy such as metformin. Specifically, the approach of up-titrating the first glucose-lowering agent and subsequently adding second and third agents may lead to a delayed intensification of pharmacotherapy due to "clinical inertia." In addition, the up-titration of monotherapy may reach beyond the maximum effective dose or increase adverse side effects. Therefore, starting more than one glucose-lowering agent earlier on in diabetes management has the potential to offer greater efficacy, with FDC providing further benefits by simplifying the dosing regimen while possibly reducing the overall cost.

Metformin is the most widely recommended first glucose-lowering agent in managing T2DM. In the US, many drug classes are available in combination with metformin as FDC. These include DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin, alogliptin), sulfonylureas (glipizide, glyburide), SGLT2 inhibitors (dapagliflozin, canagliflozin, empagliflozin), a meglitinide (repaglinide), and a TZD (pioglitazone). The prescription data from 2012 showed that 22% of metformin use was in conjunction with that of a DPP4 inhibitor. A meta-analysis of 15 randomized controlled trials evaluating initial combination therapy with metformin plus either DPP4 inhibitor, SGL2 inhibitor, or TZD versus metformin monotherapy showed that a greater proportion of patients starting on combination therapy achieved the goal HbA1C below 7% compared to those that started metformin monotherapy.[1]

In choosing an FDC, clinicians should consider the benefits and risks associated with each of the component drugs in the FDC. The combination of metformin and sulfonylurea is losing its appeal because of the risk of hypoglycemia and weight gain associated with sulfonylurea. Similarly, TZD use has declined dramatically over the years because of concerns about cardiovascular safety and possible association with increased risk of bladder cancer. SGLT2 inhibitors are promising, with added benefits of weight loss and blood pressure control. However, the US FDA released a warning in May 2015 about the potential risk of diabetic ketoacidosis resulting from SGT2 inhibitors.

For patients who cannot tolerate metformin, alternative oral combinations exist, including TZD plus sulfonylurea, TZD plus DPP4 inhibitor (eg, alogliptin and pioglitazone), SGT2 inhibitor and DPP4 inhibitor (eg, dapagliflozin plus saxagliptin, empagliflozin plus linagliptin), SGLT2 inhibitor plus sulfonylurea, and SGLT2 inhibitor plus TZD. The combination of empagliflozin and linagliptin was approved by the FDA in 2015 based on phase III studies over 52 weeks that demonstrated that the use of the FDC in treatment-naïve patients led to a significantly lower reduction in HbA1C
($P < .001$) compared to both individual components.

In terms of the cost of FDCs, a systematic review of 17 studies reported reduced direct medical costs, better health care utilization, and better adherence with FDCs compared to multiple-pill regimens.[2] Patients with insurance usually have a single copay for an FDC prescription, although some insurers may not cover certain FDCs. Therefore, clinicians are advised to consider costs of differing FDCs for each individual patient.

In summary, single-pill FDC therapies may lead to improved management of patients with T2DM by simplifying their medication regimen, reducing the pill burden and possible costs, and ultimately improving adherence to treatment. At the same time, clinicians should be familiar with the benefits and risks of each component within FDC therapy.

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FIXED-DOSE METFORMIN XR COMBINATIONS

Blonde L, San Juan ZT, Bolton P. Fixed-dose combination therapy in type 2 diabetes mellitus. *Endocr Pract*. 2014;20(12):1322-1332.

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In this review article, the authors examined the role of FDCs in the treatment of type 2 diabetes with a particular focus on the use of a once-daily regimen containing metformin extended-release (XR) as a component of the FDCs. Metformin is the first-choice monotherapy in the treatment algorithm recommended by organizations such as the American Diabetes Association, European Association for the Study of Diabetes, and American Association of Clinical Endocrinologists. Not surprisingly, metformin is the most commonly prescribed glucose-lowering medication for patients with T2DM.[1] Also, FDCs containing metformin far outnumber those not containing metformin.

Metformin XR offers several advantages over metformin immediate-release (IR), including a simpler regimen of once-daily use, more gradual release from the upper gastrointestinal tract into circulation (time to peak serum concentration of 7 versus 3 hours), and better tolerability related to the lower incidence of GI-related side effects. The authors review three FDCs containing metformin XR: saxagliptin/metformin XR, pioglitazone/metformin XR, and sitagliptin/metformin XR. In general, the FDCs have similar efficacy compared to separate-pill combination therapy, although there were no specific studies evaluating FDCs containing metformin XR at the time of this publication.[2]

Safety and tolerability data of once-daily FDCs compared to their individual component drugs suggest comparability in both aspects. Pharmacokinetic studies showed bioequivalence for each FDC with separate-pill combinations. The safety issues for each glucose-lowering medication remain the same in FDCs compared with separate-pill combinations. Metformin in either IR or XR formulation can be associated with GI side effects with no evidence of an increase in GI side effect with FDCs compared with separate-pill combinations. In treatment-naïve patients with T2DM, the safety and tolerability issues for FDCs will be similar to those with individual components rather than unique to the combinations themselves.

The authors conclude that FDCs containing metformin XR may improve adherence by simplifying the regimen and improving tolerability. While preliminary data suggest that FDCs may be cost-effective, direct patient costs may vary by insurance coverage.

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FIXED-DOSE VERSUS LOOSE-DOSE COMBINATIONS

Lokhandwala T, Smith N, Sternhufvud C, Sorstadius E, Lee WC, Mukherjee J. A retrospective study of persistence, adherence, and health economic outcomes of fixed-dose combination versus loose-dose combination of oral anti-diabetes drugs. *J Med Econ*. 2015:1-29.

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The authors of this article aimed to compare the adherence and economic outcomes between patients with T2DM using fixed-dose combination (FDC) versus loose-dose combination (LDC) products using a large national US claims data. The retrospective, observational cohort study was conducted using the Truven Health MarketScan Commercial Claims and Encounters Database, which contains employer- and health plan-sourced data with medical and drug claims over 40 million people annually, as well as the

Truven Health MarketScan Medicare Supplemental and Coordination of Benefits Database (Medicare Supplemental), containing 4.3 million inpatient and outpatient medical and prescription claims of Medicare-eligible persons with supplemental insurance plans.

The study population consisted of adults diagnosed with T2DM not on any glucose-lowering drugs during the preindex period and having at least two glucose-lowering prescriptions during follow-up. Patients were categorized into two groups, depending on the type of index glucose-lowering medication regimen: 1) FDC cohort or 2) LDC cohort. The authors excluded patients with gestational diabetes, secondary diabetes, or type 1 diabetes (T1DM). The primary outcomes were: a) persistence as defined by medication use without any gap greater than 30 days, and b) adherence to the medication regimen as measured by medication possession ratio (MPR). The MPR was calculated as the ratio between the sum of total days' supply for all fills and the number of days between the first and last fill plus days' supply of the last fill. Secondary endpoints included hypoglycemia, health care resource utilization, and costs.

A total of 23,361 patients were included in the analysis. Compared to the LDC cohort, the FDC cohort was younger and had more endocrinologist visits and lower comorbidity rates. The most popular FDCs were DPP4 inhibitor plus metformin, followed by sulfonylurea plus metformin. Compared to the LDC cohort, the FDC cohort had a significantly lower rate of nonpersistence ($P < .0001$), a higher rate of adherence ($P < .0001$), and lower rate of hypoglycemia ($P = .002$). Regarding cost, while the prescription costs were higher in the FDC cohort ($290 vs $225, $P < .001$), the all-cause monthly costs were lower in the FDC cohort compared to the LDC cohort, suggesting economic benefits beyond monthly prescription costs. These findings agree with those of previous studies conducted in the US and Italy.[1,2]

The strengths of this study include the use of a single data source to capture treatment patterns, use of definitions consistent with those in prior studies, and comparison between FDCs and corresponding LDCs (rather than a comparison of individual drugs within these classes). The study is limited by the inherent weaknesses of using claims data; for example, prescriptions filled do not equate to treatment administration, and there is lack of clinical data to understand the diabetes severity and other comorbidities in both the FDC and LDC groups. Furthermore, the results are only applicable to treatment-naïve patients. It should also be noted that the study was funded by pharmaceutical companies that make FDCs.

In summary, the use of FDCs to treat patients with T2DM may improve medication adherence and subsequent reduction in overall health care utilization costs compared to the use of LDCs.

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FIXED-DOSE SGLT2 AND DPP4 INHIBITOR COMBINATION

Kim ES, Deeks ED. Empagliflozin/linagliptin: A review in type 2 diabetes. *Drugs*. 2015;75(13):1547-1557.

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In this review article, the authors summarized pharmacological, efficacy, and tolerability data related to the use of empagliflozin/linagliptin, the first fixed-dose combination of an SGLT2 inhibitor and a DPP4 inhibitor that has been approved in the US for treatment of type 2 diabetes.

Empagliflozin inhibits SGLT2, thus blocking urinary glucose reabsorption and subsequently lowers blood glucose levels. In one study, daily use of empagliflozin for 27 days in patients with T2DM led to 45% inhibition of filtered glucose reabsorption.[1] Linagliptin inhibits DPP4, an enzyme that degrades gut hormones such as GLP-1 and GIP, thereby increasing the blood concentration of these beneficial gut hormones and subsequently stimulating glucose-dependent insulin secretion. Linagliptin significantly increased GLP-1 and GIP (p = 0.003) and reduced glucagon levels after 28 days of use (P = .045).[2] The pharmacokinetic data for fixed-dose empagliflozin/linagliptin are limited. However, the manufacturer-sponsored study that led to the FDA approval demonstrated bioequivalence of the fixed-dose combination with the individual drugs administered at equal doses.

The efficacy of empagliflozin/linagliptin was evaluated in a randomized, double-blind phase III trial in adults with T2DM. At week 24, empagliflozin/linagliptin 10 mg/5 mg lowered HbA1C and fasting blood glucose levels significantly more (P < .001) than the individual components (ie, empagliflozin 10 mg or linagliptin 5 mg); in contrast, empagliflozin/linagliptin 25 mg/5 mg was superior to linagliptin 5 mg but not versus empagliflozin 25 mg. No significant reduction in blood pressure was seen with either empagliflozin/linagliptin 10 mg/5 mg or 25 mg/5 mg daily.[3] Used as an add-on therapy to metformin, the empagliflozin/linagliptin FDC achieved better HbA1C and fasting blood glucose reductions than adding the individual components.[4]

During the 52-week trial, empagliflozin/linagliptin tolerability was similar to that of the individual components. The most common adverse effects were urinary tract infection, upper respiratory tract infection, and nasopharyngitis. Serious adverse events occurred in 6.6% of subjects receiving empagliflozin/linagliptin compared to 7.1% of those receiving empagliflozin. Serious adverse events were hypoglycemia (< 4% risk), and one case of acute pancreatitis among 137 individuals who received empagliflozin/linagliptin 25 mg/5 mg. There were no reports of patients developing acute heart failure, QT prolongation, or diabetic ketoacidosis in this trial.[4]

In conclusion, empagliflozin/linagliptin is the first SGLT2 inhibitor/DPP4 inhibitor fixed-dose combination as initial or add-on treatment for patients with T2DM. The efficacy of this combination pill is better than that of the individual components with regard to hemoglobin or fasting glucose reduction, and is similarly well tolerated compared to the individual components. The main limitation of this study is its short duration.

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DPP-4 INHIBITORS PLUS METFORMIN

Liu Y, Hong T. Combination therapy of dipeptidyl peptidase-4 inhibitors and metformin in type 2 diabetes: Rationale and evidence. *Diabetes Obes Metab*. 2014;16(2):111-117.

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In this review article, the authors provide an overview of the clinical evidence behind metformin/DPP4 inhibitor fixed-dose combinations (FDC). Studies evaluating the efficacy of combining the use of DPP4 inhibitor and metformin showed that the combination was comparable to that of sulfonylurea and metformin in terms of HbA1C reduction.

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Metformin/DPP4 FDC therapy is well-tolerated, with a low and similar incidence of hypoglycemia compared to that with metformin monotherapy. Despite a theoretical concern that the combination of metformin/DPP4 inhibitor may exacerbate GI side effects, one trial found a lower rate of GI side effects with this FDC compared to an equivalent dose of metformin monotherapy.[1] While GLP-1 agonists are more effective glucose-lowering agents than DPP4 inhibitors, they are injectable medications that cannot easily be combined with other oral medications for FDC therapy. In contrast, DPP4 inhibitors are oral medications that can be easily combined with metformin or other oral antidiabetic medications.

The authors list several reasons supporting the combined use of DPP4 inhibitor and metformin. For example, these two medications have differing mechanisms for lowering blood glucose levels and may work synergistically. Indeed, studies have shown a greater reduction in both fasting glucose and A1C using the DPP4 inhibitor/metformin FDC compared to their respective monotherapies.[2] Specifically, metformin may indirectly stimulate insulin secretion via an increase in GLP-1 secretion: data show a greater increase in GLP-1 concentrations using the DPP4 inhibitor/metformin FDC compared to their respective monotherapies, suggesting a synergistic incretin effect.[3] Mechanisms of metformin-induced GLP-1 secretion include: 1) inhibition of the apical sodium-dependent bile acid transporter, thus increasing the concentration of bile acids and subsequent stimulation of GLP-1 secretion, 2) inhibition of DPP4 activity directly by metformin, thus leading to an increase in bioactive GLP-1 concentrations, and 3) up-regulation of the GLP-1 receptor through a PPAR-alpha dependent mechanism.[4-6] Similarly, DPP4 inhibition may potentiate the glucose-lowering effect of metformin by activating the AMPK pathway (as shown in mice).[7]

In summary, metformin/DPP4 inhibitor is an effective FDC that is as well as tolerated as the individual components, while providing glucose-lowering effects that may be better than the individual components alone. The coadministration of these compounds may have additive or synergistic effects in addition to simplifying the ease of use, thus making it a promising strategy for treatment of T2DM.

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KEY TAKEAWAYS

- Achieving the glycemic goal in patients with type 2 diabetes remains a challenge, in part due to the progressive failure of beta cells, insulin resistance, ineffective lifestyle, weight gain, and cost-related poor adherence to treatment.
- An increasing number of fixed-dose combinations (FDC) for treatment of type 2 diabetes are available in the United States that can facilitate adherence and reduce health care costs.

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- FDCs may provide better efficacy and tolerability compared to their individual components, due to their additive glucose-lowering benefits and the tendency to avoid maximum dose titration.

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