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REVIEW

Fixed-Dose Combinations for Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Combining antihyperglycemic agents with complementary mechanisms of action is a cornerstone of type 2 diabetes mellitus (T2DM) management. Although several fixed-dose combinations (FDCs) are available, representing standard types of combination therapy in T2DM, use of these products has been limited. ***Methods:*** To address the likely concerns of prescribers and patients regarding the use of FDCs in the treatment of T2DM, literature searches were performed to ascertain the bioavailability, efficacy, tolerability, and cost-effectiveness of the currently approved FDCs compared with their individual component drugs given as separate pills in combination. Additionally, data were collected on rates of adherence, clinical outcomes, and overall treatment costs with FDCs versus dual therapy with the same constituent drugs. ***Results:*** Bioavailability is equivalent for FDCs and dual therapy used in T2DM. Efficacy and tolerability also appear to be at least as good with FDCs as with dual therapy. Retrospective analyses have suggested that FDCs can enhance adherence to therapy, presumably as a result of the reduction in pill burden, and improved adherence may result in improved glycemic control and reduced disease management costs. In addition, because currently available FDCs come in two or more dose-strength formulations, they also afford some measure of dosing flexibility. ***Conclusions:*** The available evidence supports the wider use of FDCs in the treatment of patients with T2DM.

Keywords: adherence; bioavailability; cost; efficacy; FDC; fixed-dose combination; glycemic control; tolerability; type 2 diabetes mellitus

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INTRODUCTION

For more than a decade, fixed-dose combinations (FDCs) of orally administered drugs have been available for the treatment of numerous disorders, including HIV, tuberculosis, hypertension, and type 2 diabetes mellitus (T2DM). These pills consist of two or more pharmaceutical compounds in a single tablet. Whereas agents used to treat infectious diseases, such as tuberculosis, are combined primarily to capitalize on synergistic effects to prevent or overcome drug resistance,[1] the usual purpose of combinations for other conditions is to employ complementary mechanisms of action to address different aspects of the disease pathophysiology. For example, in T2DM, an insulin sensitizer (metformin or a thiazolidinedione [TZD]) may be combined with an insulin secretagogue (a sulfonylurea or a meglitinide) or an incretin-based agent (a glucagon-like peptide-1 [GLP-1] receptor agonist or a dipeptidyl peptidase-4 [DPP-4] inhibitor).

The FDCs approved for treatment of T2DM in the USA (as well as the names of FDCs also available in Europe) are listed in Table 1. For most of these FDCs, bioavailability of each component drug is equivalent to that seen when coadministered as separate pills, as demonstrated for regulatory approval.[2-9] With metformin/glyburide, bioavailability of metformin is equivalent to that seen when coadministered with glyburide as separate pills; however, the area under the plasma concentration versus time curve for glyburide is higher than that seen when coadministered with metformin as separate pills.[10]

Despite the advantages FDCs can offer, their use has been relatively modest. This paper examines the use of FDCs versus separate-pill combination therapy with the same drugs for the treatment of T2DM and assesses the evidence that may address some of the concerns of prescribers, payers, and patients.

METHODS

A literature search was conducted on PubMed using the search string "fixed-dose combination" or "single-pill combination" AND "type 2 diabetes" in the title and/or abstract fields. This initial search yielded approximately 80 citations. Although the majority of these citations were primary reports, many of them were studies comparing FDCs versus monotherapy with one of the component drugs, rather than FDCs versus dual therapy with both of the component drugs, which is the focus of this review. The authors also performed supplementary searches on the trade names of each of the currently available FDCs used in T2DM and on the equivalent combinations of generic names. Preference was given to prospective and retrospective primary sources that provided data on the factors considered most likely to affect prescribers' and patients' perceptions and concerns about the use of FDCs versus dual therapy: bioavailability, efficacy, safety, tolerability, glycemic control and other clinical outcomes, adherence to treatment, and costs. Also, when deemed appropriate, the authors have cited reports on the use of FDCs in clinical areas other than T2DM, previous reviews that revealed important general principles of combination therapy with FDCs versus dual therapy, and product label information for the FDCs currently available for treatment of T2DM.

COMBINATION THERAPY IN T2DM

T2DM results from multiple pathophysiologic defects, including insulin resistance, impaired insulin secretion, and impairment in the incretin

system. Insulin resistance develops in the liver, contributing to elevated hepatic gluconeogenesis, and also in muscle and fat, where it limits glucose uptake by these tissues. Impaired insulin secretion results primarily from progressive beta-cell dysfunction and loss of beta-cell mass. Incretin impairment in T2DM involves a deficiency in GLP-1 and decreased sensitivity to the insulin-stimulatory effects of both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).[11]

Table 1. Available fixed-dose combinations (FDCs) by class and mechanism of action (*continued on next page).*

Class (targets*)	US trade name(s) (generic components: dose [mg]; frequency)	Available in Europe as:	Mechanisms of action
Metformin + sulfonylurea (A, B)	Glucovance® (Bristol-Myers Squibb, NJ, USA) (glyburide/metformin IR: 1.25/250, 2.5/500, 5/500; twice daily) Metaglip® (Bristol-Myers Squibb, NJ, USA) (glipizide/metformin IR: 2.5/250, 2.5/500, 5/500; twice daily)	–	Metformin • Improves hepatic insulin sensitivity and reduces hepatic gluconeogenesis • May improve peripheral insulin sensitivity and increase glucose uptake in muscle Sulfonylurea • Increases insulin secretion from pancreatic beta-cells
Metformin + meglitinide (A, B)	Prandimet® (Novo Nordisk, Bagsvaerd, Denmark) (repaglinide/metformin IR: 1/500, 2/500; twice daily)	–	Meglitinide • Increases insulin secretion
Metformin + DPP-4 inhibitor (A, C)	Janumet® (Merck & Co., NJ, USA) (sitagliptin/metformin IR: 50/500, 50/1000; twice daily) Kombiglyze XR® (Bristol-Myers Squibb, NJ, USA; AstraZeneca, London, UK) (saxagliptin/metformin XR: 5/500, 5/1000, 2.5/1000; once daily)	Efficib®, Janumet®, Ristfor®, Velmetia® (Merck & Co., NJ, USA) Komboglyze® (Bristol-Myers Squibb, NJ, USA)	DPP-4 inhibitor • Blocks breakdown of endogenous GLP-1 and GIP to stimulate postprandial insulin and suppress glucagon, in a glucose-dependent manner
Metformin + TZD (A)	Actoplus Met® (Takeda Pharmaceuticals, Osaka, Japan) (pioglitazone/metformin IR: 15/500, 15/850; divided doses with meals) Actoplus Met XR® (Takeda Pharmaceuticals, Osaka, Japan) (pioglitazone/metformin XR: 15/1000, 30/1000; once daily) Avandamet® (GlaxoSmithKline Plc, Brentford, UK) (rosiglitazone/metformin IR: 2/500, 4/500, 2/1000, 4/1000; divided doses with meals)	Competact®, Glubrava® (Takeda Pharmaceuticals, Osaka, Japan) – –	TZD • Improves peripheral insulin sensitivity and increases glucose uptake in muscle and fat • Improves hepatic insulin sensitivity and reduces hepatic glucose output

Table 1 ***(continued).*** Available fixed-dose combinations (FDCs) by class and mechanism of action.

Class (targets*)	US trade name(s) (generic components: dose [mg]; frequency)	Available in Europe as:	Mechanisms of action
TZD + sulfonylurea (A, B)	Avandaryl® (GlaxoSmithKline Plc, Brentford, UK) (rosiglitazone/glimepiride: 4/1, 4/2, 4/4, 8/2, 8/4; once daily)	–	
	Duetact® (Takeda Pharmaceuticals, Osaka, Japan) (pioglitazone/glimepiride: 30/2, 30/4; once daily)	Tandemact® (Takeda Pharmaceuticals, Osaka, Japan)	

*Targets: A=insulin resistance; B=impaired insulin secretion; C=impaired incretin function.
DPP-4=dipeptidyl peptidase-4; FDC=fixed-dose combination; GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; IR=immediate-release formulation; TZD=thiazolidinedione; XR=extended-release formulation.

Using monotherapy to target a single defect is often inadequate to achieve glycemic goals, and the result is prolonged exposure to hyperglycemia and an increased risk of diabetic complications.[11-14] Consequently, combination therapy using agents with complementary mechanisms of action has become a cornerstone of T2DM management.

The algorithm created for the American Diabetes Association and European Association for the Study of Diabetes recommends combination therapy for all patients with glycated hemoglobin (A1C) >7% after 2-3 months of metformin monotherapy.[15] An algorithm created for the American Association of Clinical Endocrinologists and the American College of Endocrinology advises combination therapy when oral monotherapy fails to achieve or maintain A1C ≤6.5% after 2-3 months and consideration of combination therapy at the time of diagnosis for patients with A1C >7.5%.[16] However, both algorithms emphasize the importance of individualizing glycemic goals based on a number of factors, including duration of diabetes, life expectancy, history of significant hypoglycemia or hypoglycemia unawareness, and presence of extensive comorbid conditions or advanced diabetic complications, including cardiovascular disease.

Combination antihyperglycemic pharmacotherapy will eventually be necessary for the majority of patients with T2DM, owing to the progressive nature of the disease.[15,16] Furthermore, because these patients often have hypertension, dyslipidemia, and other comorbidities that require pharmacotherapy,[17] patients are likely to be taking multiple medications even before antihyperglycemic pharmacotherapy is initiated. Thus, polypharmacy is a frequent problem in this population, and the use of FDCs is a rational approach to achieving and maintaining glycemic control while minimizing what may already be a heavy pill-burden for the patient.

USE OF FDCs IN T2DM

To date, 10 FDCs have been approved for use in the treatment of T2DM in the USA (Table 1). Despite their utility and convenience, FDCs

are used by only a minority of eligible patients. Some reports show that combination therapy using separate pills is 2-3 times more common than the use of FDCs.[18,19] Among patients switching from monotherapy to combination therapy, the number who went to separate-pill combinations was >4 times greater than the number who went to FDCs (*n*=2518 vs. *n*=543); and among patients who were already on separate-pill combination therapy, the number who stayed on dual therapy was >46 times greater than the number who switched to FDCs (*n*=13,145 vs. *n*=284).[20] In another report, >17 times more patients switched from monotherapy to combination therapy were prescribed dual therapy rather than FDCs (*n*=1815 vs. *n*=105).[21]

There are several possible explanations for the relatively low use of FDCs. Prescribers may perceive difficulty in dose titration and adjustment, and in attributing adverse events to a specific component drug. Payers, managed-care organizations, and formulary managers may be concerned about costs. A survey of patients' attitudes about FDCs[22] revealed concerns about pill size, lack of flexibility in dose timing, potential allergies, and marginal reduction in pill burden if they were taking numerous other medications for comorbid conditions. In addition, patients who are satisfied taking separate pills in combination may see no reason to change.

ADDRESSING CONCERNS REGARDING THE USE OF FDCs FOR T2DM

Therapeutic Effectiveness

Therapeutic effectiveness with FDCs is generally equivalent to combination therapy with their component drugs given as separate pills. As shown in Table 2,[23-30] reductions in A1C and fasting glucose are greater with FDCs[23-27] and with dual therapy[28-30] than with monotherapy.

Some FDCs may offer an efficacy advantage over combination treatment with separate pills, although this has not been confirmed by prospective randomized trials. In a 2010 report by Thayer et al., a retrospective analysis of data from 16,490 managed-care patients with T2DM showed significant improvements in adherence ($P<0.001$) and reductions in A1C ($P=0.004$) in patients who switched from separate-pill combination therapy to an FDC versus those who continued on separate-pill regimens.[20] Similarly, a retrospective study in 1421 patients showed significantly greater improvement in A1C with a metformin/glyburide FDC than with coadministration of separate pills, despite the fact that mean dosages were significantly lower with the FDC. Use of the FDC was also associated with significantly greater adherence, although there was no significant correlation between improved adherence and improved A1C.[31]

Tolerability

Tolerability is comparable with combination therapy delivered as an FDC or as separate pills because the dosage is often similar with both regimens (Table 3).[23-30] The perception that it is difficult to attribute adverse effects to a particular component of an FDC may be valid in the case of initial combination therapy in a drug-naive patient, but that concern would also apply to dual therapy. For patients who have switched from monotherapy to dual therapy by adding a second drug, a switch from dual therapy to a comparable regimen delivered via an FDC would not be expected to cause new tolerability issues.

Dosing Flexibility

The currently available FDCs for use in patients with T2DM are formulated in a variety of useful dosage combinations, as shown in Table 1. It should be kept in mind that dosing flexibility with individually administered drugs is limited to combinations reflecting the available formulations of each drug.

Adherence

Approximately 50% of patients with chronic diseases show poorer-than-expected responses to prescribed medication because of inadequate adherence,[32] a problem that applies to patients with T2DM.[33-35] In chronic, complex conditions in which polypharmacy is common, a reduction in pill burden could potentially enhance adherence,[36] which may be achieved with FDCs.[18,19,37-40]

In a retrospective analysis of outcomes among more than 11,000 diabetic patients in a managed-care organization, nonadherence to oral antihyperglycemic medication (administered in <80% of the total number of days covered by filled prescriptions) was associated with statistically significant (P<0.001) increases in all-cause mortality and all-cause hospitalization; conversely, each 25% increase in adherence to antihyperglycemic medication was associated with a 0.05% decrease (95% CI, –0.08 to –0.01) in A1C.[35] Similarly, analyses of pharmacy claims

Table 2. Effects of combination versus monotherapy on glycemic parameters in patients with type 2 diabetes mellitus (T2DM) for two-drug regimens now available in fixed-dose combinations (FDCs) *(continued on next page)*.

Treatment[reference]	Maximum daily doses, mg (via titration as per protocol)	A1C, %		Fasting plasma glucose, mg/dL	
		Baseline	Change	Baseline	Change
Glucovance® (metformin + glyburide) 20-week study of initial FDC therapy[23]	MET 1000/GLY 5	8.25	–1.48*	177	–42†
	MET 2000/GLY 10	8.18	–1.53*	175	–40†
	MET 2000	8.26	–1.03	176	–21
	GLY 10	8.21	–1.24	179	–36
	Placebo	8.21	–0.21	177	+5
Actoplus Met® (pioglitazone + metformin) 24-week study of initial FDC therapy[24]	PIO 30/MET 1700	8.89	–1.83‡	177.5	–39.9*
	PIO 30	8.69	–0.96	170.8	–22.2
	MET 1700	8.65	–0.99	170.5	–24.8
Avandamet® (rosiglitazone + metformin) 32-week study of initial FDC therapy[25]	ROSI 8/MET 2000	8.9	–2.3‡	202	–74‡
	ROSI 8	8.8	–1.6	193	–47
	MET 2000	8.8	–1.8	198	–50
Avandaryl® (rosiglitazone + glimepiride) 28-week study of initial FDC therapy[26]	ROSI 4/GLIM 4	9.0	–2.41‡	207	–70‡
	ROSI 8/GLIM 4	9.2	–2.52‡	214	–80‡
	ROSI 8	9.1	–1.75	212	–57
	GLIM 4	9.0	–1.72	211	–42
Metaglip® (glipizide + metformin) 18-week study of initial FDC therapy[27]	GLIP 20/MET 2000	8.7	–1.3§	194	NR§
	GLIP 30	8.9	–0.4	204	NR
	MET 2000	8.7	–0.2	191	NR

Table 2 ***(continued)*****.** Effects of combination versus monotherapy on glycemic parameters in patients with type 2 diabetes mellitus (T2DM) for two-drug regimens now available in fixed-dose combinations (FDCs).

Treatment[reference]	Maximum daily doses, mg (via titration as per protocol)	A1C, %		Fasting plasma glucose, mg/dL	
		Baseline	Change	Baseline	Change
Metformin + repaglinide (now available as Prandimet®) 16- to 20-week study of repaglinide added to ongoing metformin (individual pills)[28]	MET ~1800‖/REPAG 4	8.3	−1.41¶	184	−39.3¶
	MET ~1800‖	8.6	−0.33	195	−4.5
	REPAG 4	8.6	−0.38	174	+8.6
Sitagliptin + metformin (now available as Kombiglyze XR®#) 24-week study of initial dual combination therapy (individual pills)[29]	SAXA 5/MET 2000	9.4	−2.5**	199	−60††
	SAXA 10/MET 2000	9.5	−2.5**	204	−62**
	SAXA 10	9.6	−1.7	201	−31
	MET 2000	9.4	−2.0	198	−47
Sitagliptin + metformin (now available as Janumet®) 24-week study of initial dual combination therapy (individual pills)[30]	SITA 100/MET 1000	8.79	−1.40§	203.9	−47.1§
	SITA 100/MET 2000	8.76	−1.90§	196.7	−63.9§
	SITA 100	8.87	−0.66	201.4	−17.5
	MET 1000	8.90	−0.82	205.2	−27.3
	MET 2000	8.68	−1.13	197.0	−29.3
	Placebo	8.68	+0.17	196.3	+5.8

*P<0.01 versus all monotherapies.
†P≤0.001 versus MET monotherapy.
‡P<0.0001 versus all monotherapies.
§P≤0.001 versus all monotherapies.
‖Prestudy dosage of MET maintained. Mean daily MET dose presented.
¶P<0.05 versus all monotherapies.
#SAXA is not approved at 10 mg; Kombiglyze XR is available with SAXA 2.5 mg plus MET 1000 mg or with SAXA 5 mg plus MET 500 or 1000 mg.
**P<0.0001 versus MET monotherapy.
††P=0.0002 versus MET monotherapy.
A1C=glycated hemoglobin; GLIM=glimepiride; GLIP=glipizide; GLY=glyburide; MET=metformin; NR=value not reported; PIO=pioglitazone; REPAG=repaglinide; ROSI=rosiglitazone; SAXA=saxagliptin; SITA=sitagliptin; XR=extended-release formulation.

for patients with T2DM have revealed that a 10% poorer score on an adherence measure corresponds with a 0.14% increase in A1C.[34]

Among patients with T2DM using combination therapy, adherence tends to be greater with FDCs than with separate pills[21,31] and greater after switching from monotherapy to an FDC rather than to separate-pill combinations.[18,19,21] In the previously cited retrospective analysis by Thayer et al., adherence rates declined slightly among patients who were switched from monotherapy to combination therapy, but the decline was significantly smaller when switching to an FDC versus switching to separate-pill combinations.[20] In contrast, among patients who were already using separate-pill combinations, adherence improved significantly when switching to an FDC.

Treatment adherence tends to improve with drug regimens that are simplified by reducing the number of pills[41-43] and reducing dosing frequency.[44,45] By definition, all FDCs result

Table 3. Selected adverse events reported with fixed-dose combinations (FDCs) in patients with type 2 diabetes mellitus (T2DM).

Treatment[reference]	Maximum daily doses, mg (via titration as per protocol)	Incidence, %				
		Nausea/ vomiting	Diarrhea	Abdominal pain	Headache	Hypo-glycemia*
Glucovance® (metformin + glyburide) 20-week study of initial FDC therapy [23]	MET 1000/GLY 5	1.9	7.6	5.7	NR	5.1
	MET 2000/GLY 10	4.9	12.3	5.6	NR	16.0
	MET 2000	6.3	15.1	5.0	NR	0
	GLY 10	0.6	4.4	3.1	NR	6.3
	Placebo	4.3	3.1	1.9	NR	0.6
Actoplus Met® (pioglitazone + metformin) 24-week study of initial FDC therapy[24]	PIO 30/MET 1700	NR	9.0	2.0	5.5	1.0
	PIO 30	NR	2.6	1.6	2.6	0.5
	MET 1700	NR	15.3	3.3	4.8	1.4
Avandamet® (rosiglitazone + metformin) 32-week study of initial FDC therapy[25]	ROSI 8/MET 2000	16	14	NR	11	0.6
	ROSI 8	8	7	NR	10	0
	MET 2000	13	21	NR	12	1.3
Avandaryl® (rosiglitazone + glimepiride) 28-week study of initial FDC therapy[26]	ROSI 4/GLIM 4	NR	NR	NR	~4.4	3.6
	ROSI 8/GLIM 4	NR	NR	NR	across	5.5
	ROSI 8	NR	NR	NR	groups	0.4
	GLIM 4	NR	NR	NR		4.1
Metaglip® (glipizide + metformin) 18-week study of initial FDC therapy[27]	GLIP 20/MET 2000	8.0	18.4	5.7	12.6	12.6
	GLIP 30	6.0	13.1	8.3	6.0	0
	MET 2000	8.0	17.3	6.7	5.3	1.3
Metformin + repaglinide (now available as Prandimet®) 16- to 20-week study of repaglinide added to ongoing metformin (individual pills)[28]	MET ~1800†/REPAG 4	NR	18.5	NR	22.2	4.9
	MET ~1800†	NR	29.6	NR	14.8	all groups
	REPAG 4	NR	7.1	NR	10.7	combined
Saxagliptin + metformin (now available as Kombiglyze XR*‡) 24-week study of initial dual therapy (individual pills)[29]	SAXA 5/MET 2000	NR	6.9	NR	7.5	0.0
	SAXA 10/MET 2000	NR	9.6	NR	9.9	0.6
	SAXA 10	NR	3.0	NR	6.3	0.0
	MET 2000	NR	7.3	NR	5.2	0.3
Sitagliptin + metformin (now available as Janumet®) 24-week study of initial dual therapy (individual pills)[30]	SITA 100/MET 1000	5.3	6.3	2.6	NR	1.1
	SITA 100/MET 2000	8.8	8.8	3.3	NR	2.2
	SITA 100	1.1	2.8	3.4	NR	0.6
	MET 1000	2.7	4.9	2.7	NR	0.5
	MET 2000	9.3	10.4	4.9	NR	1.1
	Placebo	1.7	4.0	2.3	NR	0.6

*Defined as symptoms and blood glucose ≤50 mg/dL in the studies of MET/GLY, GLIP/MET, MET/REPAG, and SAXA/MET, as symptoms and/or blood glucose <60 mg/dL in the study of PIO/MET, and as "events" in the study of SITA/MET.
†Prestudy dosage of MET maintained. Mean daily MET dose presented.
‡SAXA is not approved at 10 mg; Kombiglyze XR is available with SAXA 2.5 mg plus MET 1000 mg or with SAXA 5 mg plus MET 500 or 1000 mg.
GLIM=glimepiride; GLIP=glipizide; GLY=glyburide; MET=metformin; NR=value not reported; PIO=pioglitazone; REPAG=repaglinide; ROSI=rosiglitazone; SAXA=saxagliptin; SITA=sitagliptin; XR=extended-release formulation.

in reduced numbers of pills compared with the equivalent combination of separate pills. Older FDCs containing immediate-release metformin require twice-daily dosing to ensure adequate plasma levels of metformin;[2-6,10] whilst newer FDCs (pioglitazone plus extended-release metformin,[6] saxagliptin plus extended-release metformin,[9] and a TZD [rosiglitazone or pioglitazone] plus glimepiride[7,8]) can be administered once daily.

Cost-Effectiveness

The estimated total of direct and indirect costs of diabetes in the USA was $174 billion in 2007 (most recent data available).[46] In a systematic review, inadequate adherence to treatment for diabetes was linked to more healthcare utilization and higher costs (although the review also revealed wide methodologic variability among cost-effectiveness studies).[47] Conversely, improved adherence has been associated with lower costs in treating dyslipidemia.[38] Thus, because FDCs for T2DM can facilitate adherence and thereby reduce the long-term risk of complications and emergencies requiring hospitalization, they have the potential to reduce overall expenditures for patients with T2DM.

In terms of the cost of the medications, an analysis of Texas Medicaid payments showed that branded FDCs were significantly ($P<0.001$) less expensive than regimens consisting of the branded component medications taken separately.[19] It should be noted, however, that a branded FDC would almost certainly be more expensive than generics taken as separate pills. Similarly, in hypertension, prescription costs for FDCs versus the component drugs obtained separately were higher with respect to patients' out-of-pocket expenses, but lower with respect to total expenses paid by governmental or private third-party payers.[48]

Another report in hypertension showed reduced overall medical expenditures associated with use of an FDC, largely owing to decreased hospitalization.[49] In addition, among hypertensive patients being treated with FDCs, adherence was greater and costs were lower with continued use of FDCs rather than with switching to separate-pill combinations.[50]

CONCLUSION

Because regulatory approval of FDCs is based on bioavailability data, similar to the way generic medications are approved, the lack of prospective, randomized controlled trials directly comparing FDCs with their component drugs administered as separate pills should not be considered a limitation to their use. Although the studies reviewed here are of relatively short duration, there is no reason to believe that the effects of long-term treatment with FDCs would differ from the effects of long-term dual therapy with their component drugs given as separate pills for the treatment of T2DM, as has previously been reported in peer-reviewed literature. An area where more research is needed involves the direct comparison of drug acquisition costs and total treatment costs with brand-name FDCs versus component drugs given as separately administered generics, as the currently available data are limited.

The purpose of this review was to address any false perceptions on the part of physicians, patients, or payers that may affect utilization of FDCs for the treatment of T2DM. Based on the authors' review of the published literature, it is apparent that FDCs offer several advantages over combination therapy delivered by separate pills. For therapeutic effectiveness and tolerability, FDCs are at least equal to the same medications when taken separately. In addition, FDCs are available

in different dosage strength formulations, which allows for flexibility in selecting and adjusting dosages. Finally, greater convenience (decreased pill burden and, for some FDCs, once-daily dosing) may lead to improved adherence, which may yield superior clinical outcomes and greater cost-effectiveness.

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