TYPE 2 DIABETES TREATMENT PATTERNS IN MISSISSIPPI MEDICAID

BACKGROUND

The American Diabetes Association's (ADA's) annually updated "Standards of Medical Care in Diabetes," referred to as the "Standards of Care," is intended to provide clinicians, patients, researchers, payers, and other interested individuals with the components of diabetes care, general treatment goals, and tools to evaluate the quality of care. The Standards of Care recommendations are not intended to preclude clinical judgement and must be applied in the context of excellent clinical care, with adjustments for individual preferences, comorbidities, and other patient factors. The "Standards of Medical Care in Diabetes – 2017" [1] recommend the following regarding pharmacologic therapy for Type 2 diabetes (T2DM):

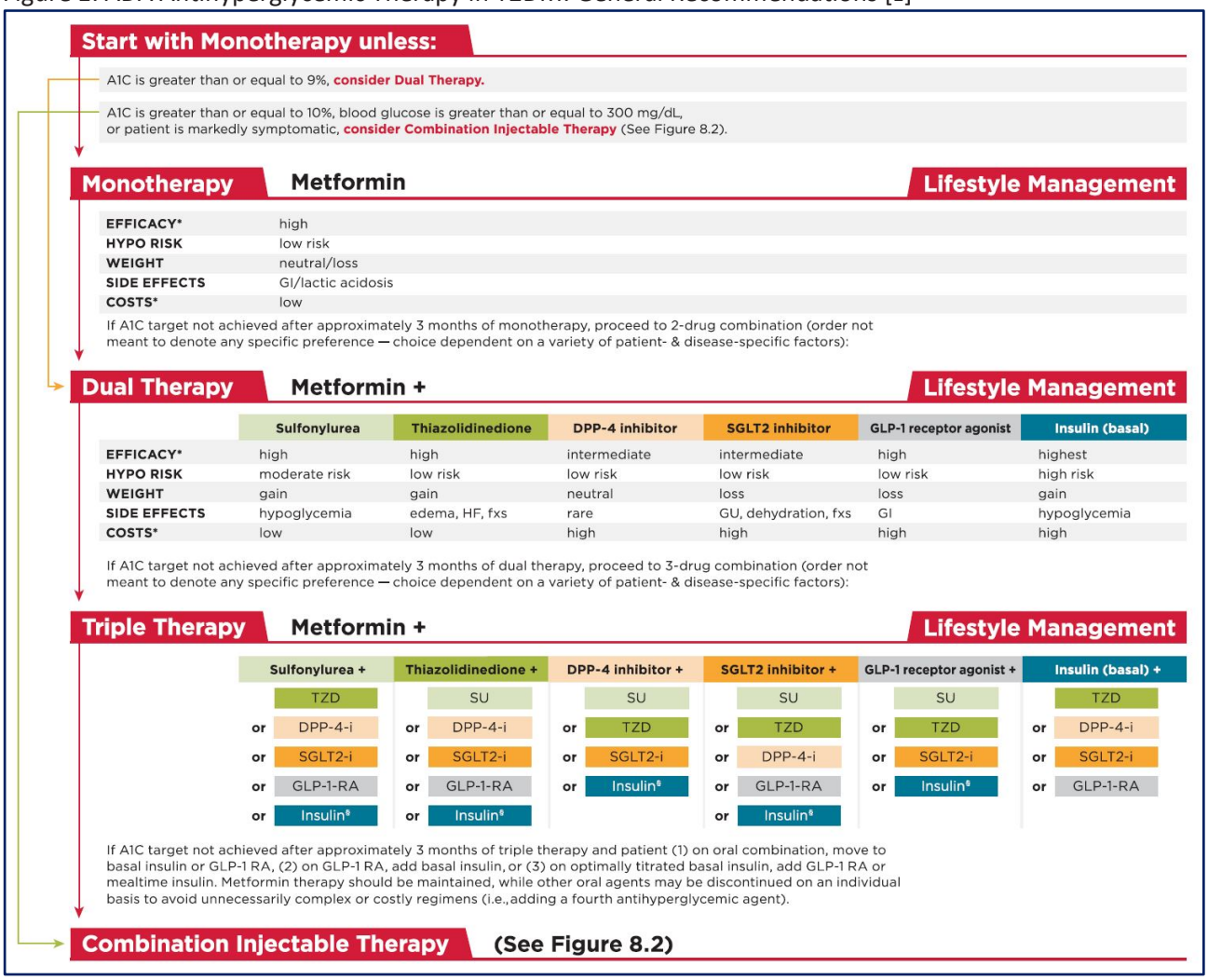
- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for the treatment of T2DM.
- Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy.
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed T2DM who are symptomatic and/or have A1C ≥ 10% (86 mmol/mol) and/or blood glucose levels ≥300 mg/dL (16.7 mmol/L).
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target after 3 months, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin.
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include efficacy, hypoglycemia risk, impact on weight, potential side effects, cost, and patient preferences.
- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed.
- In patients with long-standing suboptimally controlledT2DM and established atherosclerotic cardiovascular disease, the sodium glucose cotransportor-2 inhibitors (SGOT-2) empagliflozin (Jardiance) or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes.

As noted above, metformin if not contraindicated and if tolerated, is the preferred agent for the treatment of T2DM. In patients with metformin contraindications or intolerance, providers should consider an initial drug from another class depicted in Figure 1 under "Dual Therapy" and proceed accordingly. When A1C is ≥9%, initiating dual combination therapy should be considered to achieve the target A1C more expeditiously.

---

1 American Diabetes Association. Standards of Medical Care in Diabetes – 2017. *Diabetes Care* Volume 40, Supplement 1, January 2017. http://professional.diabetes.org/sites/professional.diabetes.org/files/media/dc_40_s1_final.pdf

Figure 1: ADA Antihyperglycemic Therapy in T2DM: General Recommendations [1]



Although there are numerous trials comparing dual therapy with metformin alone, few directly compare drugs as add-on therapy. A comparative effectiveness metaanalysis [2] suggested that each new class of non-insulin agents added to initial therapy generally lowers A1C approximately 0.9–1.1%. Other noninsulin products should be added if necessary to achieve appropriate treatment goals. The order of products in each row of the chart was determined by historical availability and the route of administration, with injectables to the right. It is not meant to denote any specific preference within each line of therapy. Potential sequence of antihyperglycemic therapy for patients with Type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). Drug choice is based on patient preferences, various patient disease, and drug characteristics with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia.

2 Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011;154:602–613

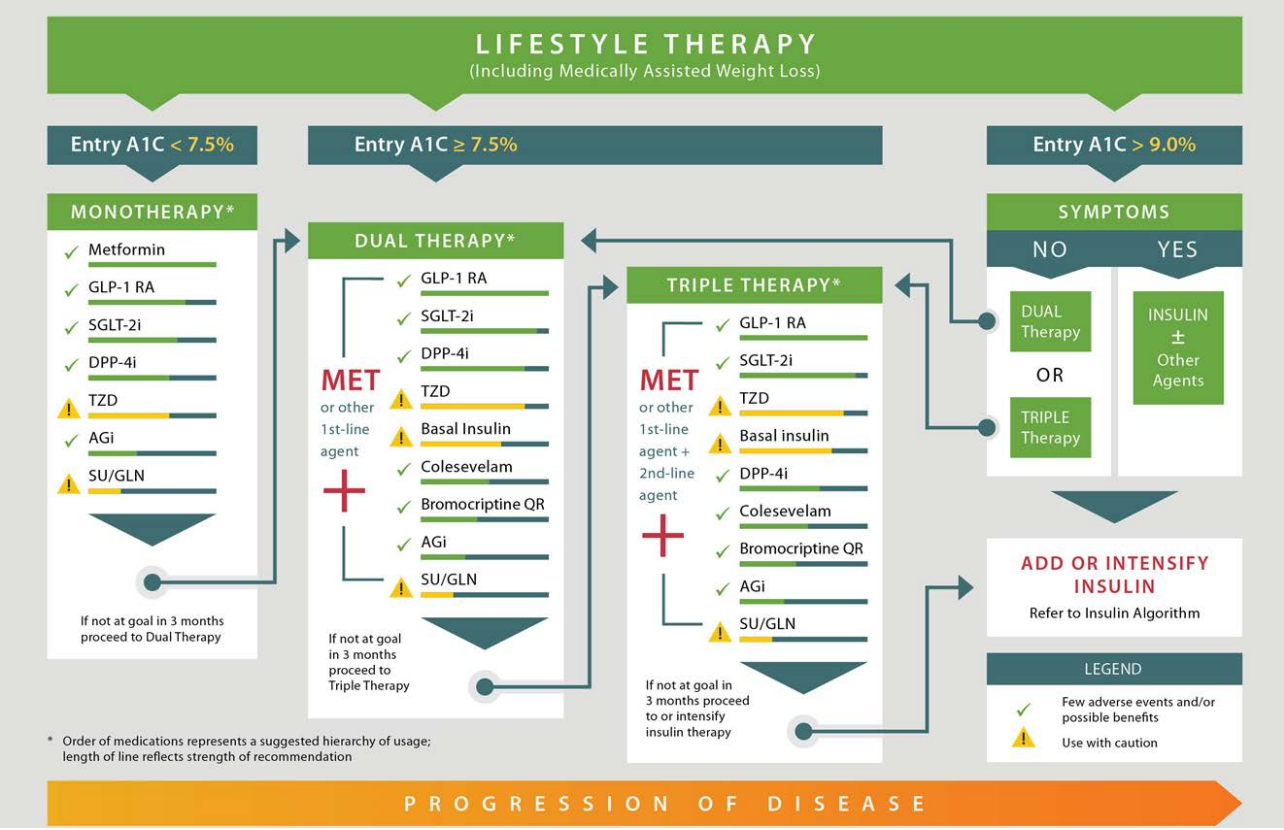
As noted in the triple therapy section in Figure 1, the ADA's Standards of Care recommend that if the A1C target is not achieved after approximately three months of triple therapy and the patient is:

1. On oral combination, should move to basal insulin or GLP-1 receptor agonist (RA)
2. On combination with GLP-1RA, should add basal insulin
3. On combination with optimally titrated basal insulin, should add GLP-1RA or mealtime insulin.

ADA's Standards of Care recommend upon advancing to next line of therapy, metformin therapy should be maintained while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) 2017 algorithm for glycemic control is shown in Figure 2.[3] This algorithm stratifies choice of therapies based on initial A1C level. It provides guidance as to what therapies to initiate and add but respects individual circumstances that could lead to different choices.

Figure 2: AACE/ACE Glycemic Control Algorithm-2017[3]



3 Consensus Statement by The American Association Of Clinical Endocrinologists And American College Of Endocrinology On The Comprehensive Type 2 Diabetes Management Algorithm – 2017 Executive Summary. Endocrine Practice Vol 23 No. 2 February 2017.

The AACE/ACE algorithm recognizes that combination therapy is usually required and should involve agents with complementary mechanisms of action. The order of agents in each column of the Glycemic Control Algorithm (Figure 2) suggests a hierarchy of recommended usage, and the length of each line reflects the strength of the expert consensus recommendation. Each medication's properties should be considered when selecting a therapy for individual patients.

MS-DUR examined the regimens used to treat beneficiaries with T2DM during 2016 in order to determine how treatment patterns may need to change based on the 2017 ADA Standards of Care and the AACE/ACE algorithm. The objectives were:

1. To evaluate how well recent treatment patterns comply with recommendations in the ADA Standards of Care and the AACE/ACE treatment algorithm.

2. To identify any utilization management actions that may be needed to improve compliance with the current recommendations.

METHODS

MS-DUR conducted a retrospective analysis using Division of Medicaid (DOM) pharmacy and medical claims from all programs including fee-for-service (FFS) and coordinated care organizations (CCOs) for the period July 1, 2015 – December 31, 2016.

Beneficiaries meeting the following criteria were included in the analyses:

- Had at least one medical claim with a diagnosis code for Type 2 diabetes during 2016, and
- Were enrolled in Medicaid for three or more months in 2016.

Claims from the last six months of 2015 and the first half of 2016 were used to identify beneficiaries that were "**new starts**" on antihyperglycemic medications. Beneficiaries were classified as new starts in 2016 if they met the following criteria:

- Had one or more claims for antihyperglycemic medications in 2016,
- Were enrolled in Medicaid for the six months prior to their first antihyperglycemic medication claim in 2016, and
- Had no previous claim for an antihyperglycemic medication during the six months prior to their first prescription in 2016.

Identifying treatment regimens: MS-DUR used refill patterns for medications in each antihyperglycemic drug class to determine regimens used to treat beneficiaries. This was accomplished by determining drug coverage patterns for each day during the observation period for 2016. For each prescription dispensed, the beneficiary was considered to be on treatment with the medication from the date of the prescription fill through the fill date plus the number of days supply dispensed. Coverage from prescription fills for drugs in the same class were combined so

that beneficiaries were considered to be "treated" with a drug class from the date of the first prescription fill in the class to (1) the end of medication possession for the last prescription fill in the class or (2) the beginning of a gap in coverage for the class of 45 days or more. Coverage gaps of 45 days or more were classified as non-persistence and beneficiaries were not considered to be on treatment during these periods. During coverage gaps less than 45 days, beneficiaries were considered to still be treated with the drug class. For each day during the observation year, coverage for each class was combined to identify the regimen being used to treat the patient. Transitioning from one regimen to another can produce short periods of false regimen combinations. Regimens that were continuously used for less than 30 days were eliminated from the analysis.

RESULTS

Demographic characteristics of beneficiaries having medical claims with diagnosis codes for T2DM are summarized in Table 1. Beneficiaries with T2DM were twice as likely to be female and more likely to be African American and the majority were age ≥45 years. However, 5,455 beneficiaries between the ages of 19 to 44 were identified as having T2DM. Almost all of the beneficiaries age 65 and older were in FFS and represent dual-eligible beneficiaries for whom DOM may not have complete prescription records due to coverage for most drugs through Medicare Part D.

TABLE 1: Characteristics of Beneficiaries Having Medical Claims Including Type 2 Diabetes Diagnoses in 2016

		FFS	UHC	MAG	TOTAL
Total		11,220	5,987	8,195	25,402
Gender*	Female	7,501	4,227	6,028	17,756
	Male	3,718	1,760	2,167	7,645
Age at End of Year	12 or less	24	111	108	243
	13 - 18	87	307	311	705
	19 - 44	892	1,978	2,585	5,455
	45 - 64	5,083	3,482	5,015	13,580
	65+	5,134	109	176	5,419
Race	Caucasian	3,584	1,723	2,263	7,570
	Afr. Amer.	6,813	3,648	5,017	15,478
	Hispanic	75	37	43	155
	Amer. Indian	112	12	15	139
	Other	636	567	857	2,060

** Gender categories do not sum to TOTAL for some programs due to missing data.*

Table 2 summarizes all of the regimen combinations that appeared as treatments in 2016. Green highlighted regimens include metformin. The ADA guidelines recommend combinations of no more than 3 antihyperglycemic drug classes; therefore, regimens including four or more classes are marked with red borders. It is unlikely that the combination of a GLP-1 receptor agonist and a DPP-4inhibitor would have an additive benefit due to that both classes affect GLP-1 concentrations though it has not been directly studied in trials. This is extremely unlikely to be cost effective. Regimens including this combination are highlighted in orange.

If it is assumed that non-insulin regimen combinations without metformin occurred due to contraindications or intolerance of metformin in the beneficiary, the majority of the treatment regimens utilized in 2016 were consistent with the ADA guidelines. Very few regimen combinations were used that directly conflicted with the ADA Standards of Care-2017 (highlighted in orange and red). Possible areas for improvement may exist that would require more detailed analyses of individual patient cases. These areas include:

1. The large number of beneficiaries (n = 719) treated with insulin only when the ADA guidelines recommend metformin as initial therapy and its use be continued when possible.
2. Medications in one class being titrated to maximum doses prior to the addition of a drug from a different pharmacological class.
3. The use of sulfonylureas as monotherapy especially in the newly diagnosed and treated T2DM beneficiary.

TABLE 2: All Antihyperglycemic Regimens* Used to Treat Type 2 Diabetics in 2016

Regimen*	FFS	UHC	MAG	TOTAL
MTF	1,570	209	258	2,037
MTF / DPP	248	27	27	302
MTF / DPP / GLP	2	0	1	3
MTF / GLP	11	0	3	14
MTF / SLF	283	34	49	366
MTF / SLF / DPP	39	5	1	45
MTF / SLF / DPP / GLP	0	0	1	1
MTF / SLF / GLP	2	0	0	2
MTF / SLF / TZD	3	1	0	4
MTF / SLF / TZD / DPP	3	0	0	3
MTF / SLF / TZD / DPP / AGI	1	0	0	1
MTF / TZD	19	0	3	22
MTF / TZD / DPP	5	1	0	6
SLF	564	65	90	719
SLF / DPP	48	9	5	62
SLF / DPP / GLP	5	0	0	5
SLF / GLP	3	1	0	4
SLF / TZD	18	0	2	20
SLF / TZD / DPP	1	0	0	1
TZD	53	4	0	57
TZD / DPP	4	0	0	4
TZD / GLP	1	0	0	1
AGI	2	0	0	2
DPP	246	24	38	308
DPP / AGI	5	0	0	5
DPP / GLP	2	2	0	4
GLP	46	6	6	58
INS	1,972	229	392	2,593
INS / DPP	104	5	4	113
INS / DPP / GLP	1	0	0	1
INS / GLP	28	1	2	31
INS / **MTF**	319	24	41	384
INS / **MTF** / DPP	64	5	6	75
INS / **MTF** / DPP / GLP	4	0	0	4
INS / **MTF** / GLP	4	1	0	5
INS / **MTF** / SLF	70	2	2	74
INS / **MTF** / SLF / DPP	9	0	2	11
INS / **MTF** / SLF / TZD / DPP / AGI	1	0	0	1
INS / **MTF** / TZD / DPP	6	0	0	6
INS / SLF	122	5	8	135
INS / SLF / DPP	9	2	0	11
INS / SLF / GLP	2	0	0	2
INS / SLF / TZD	1	0	0	1
INS / TZD	15	0	1	16
INS / TZD / DPP	3	0	0	3
INS / TZD / GLP	1	0	0	1

Includes metformin

Includes DPP and GLP

Includes more than 3 classes

Drug Class Abbreviations Used	
AGI	alpha-glucosidase inhibitors
DPP	DPP-4 inhibitor
GLP	GLP-1 receptor agonist
INS	insulin (all types)
MET	metformin
SGLT	SGLT-2 inhibitors
SLF	sulfonylureas
TZD	thiazolidineiones

** Only includes drug therapy coverage combinations used to treat patients continuously for 30 or more days.*

Table 3 lists the regimen combinations used as **first line therapy** for beneficiaries classified as "new starts" on pharmacologic treatment in 2016. The 2017 ADA guidelines recommend that when A1C is ≥ 9% (75 mmol/mol) dual combination therapy should be considered for first line to more expeditiously achieve the target A1C level. They also note that insulin should be considered as part of any initial combination regimen when blood glucose is ≥ 300 mg/dL (16.7 mmol/L), or A1C is ≥ 10% (86 mmol/mol), or if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia). The first line regimens included in Table 3 appear to be consistent with the ADA Standards of Care with the possible exception of a large number of patients starting on insulin without metformin.

TABLE 3: Antihyperglycemic Regimens*
Used FIRST LINE To Treat NEW STARTS in 2016

Regimen*	FFS	UHC	MAG	TOTAL
MTF	228	64	90	382
MTF / DPP	27	7	9	43
MTF / DPP / GLP	1	0	0	1
MTF / GLP	1	0	2	3
MTF / SLF	36	10	11	57
MTF / SLF / DPP	1	1	0	2
MTF / SLF / TZD	0	1	0	1
MTF / TZD	0	0	1	1
SLF	83	13	24	120
SLF / DPP	3	4	2	9
SLF / TZD	0	0	1	1
TZD	5	2	0	7
DPP	18	6	12	36
GLP	5	1	3	9
INS	196	77	119	392
INS / DPP	6	3	2	11
INS / **MTF**	22	7	12	41
INS / **MTF** / DPP	5	3	1	9
INS / **MTF** / SLF	1	0	2	3
INS / **MTF** / SLF / DPP	2	0	1	3
INS / SLF	10	1	3	14
INS / SLF / DPP	0	1	0	1
INS / TZD	1	0	1	2
INS / TZD / GLP	1	0	0	1

** Only includes drug therapy coverage combinations used to treat patients continuously for 30 or more days.*

Includes metformin
Includes DPP and GLP
Includes more than 3 classes

Drug Class Abbreviations Used	
AGI	alpha-glucosidase inhibitors
DPP	DPP-4 inhibitor
GLP	GLP-1 receptor agonist
INS	insulin (all types)
MET	metformin
SGLT	SGLT-2 inhibitors
SLF	sulfonylureas
TZD	thiazolidineiones

In assessing the potential for utilization management actions to improve treatment, it is important to determine the number of providers and beneficiaries that could be affected by any action. Table 4 shows the number of unique beneficiaries and prescribers associated with the three criteria considered to be inconsistent with the ADA Standards of Care or not cost effective.

- Only 10 beneficiaries and 10 prescribers were associated with regimens including a GLP-1 and a DPP-4.
- Only 14 beneficiaries and 15 prescribers were associated with regimens including 4 or more drug classes.
- The use of regimens that do not include metformin affected the greatest number of beneficiaries (1,939) and prescribers (239).

TABLE 4: Number of Beneficiaries and Prescribers Associated With Regimens Not Consistent With ADA Guidelines

	Beneficiaries	Prescribers
Regimen with GLP and DPP	10	10
Regimen with 4+ drug classes	14	15
Regimen without MET	1,939	239

Although the large number of regimens that did not include metformin may represent an area of concern, it is not possible from claims data to determine how often metformin is contraindicated or could not be tolerated.

CONCLUSIONS AND RECOMMENDATIONS

It appears that most of the regimens currently being used to treat beneficiaries with Type 2 diabetes are consistent with the ADA Standards of Care-2017 recommendations for pharmacological management of T2DM. The major area of concern is whether metformin is being used as often as possible. The use of regimens including both GLP-1 and DPP-4 and the use of regimens with four or more drug classes appear to be infrequent problems.

Recommendations:

1. DOM should implement an electronic edit to require manual prior authorization (PA) for concomitant use of GLP-1 and DPP-4.
2. DOM should implement an electronic edit to require manual PA for addition of fourth concurrent antihyperglycemic agents.
3. DOM should investigate regimens that do not include metformin.
4. DOM should investigate further T2DM treatment with only a sulfonylurea agent.

5. MS-DUR should conduct a one-time educational mailing highlighting the new ADA guidelines directed to prescribers who have had patients in the last year with regimens that were not consistent with the ADA Standards of Care recommendations.
6. MS-DUR should explore collaboration with the Mississippi Diabetes Coalition for educational initiatives.