Treatment Algorithms and the Pharmacological Management of Type 2 Diabetes

Mona M. Chitre, PharmD, CGP, and Susan Burke, RN, BSN, CDE

Abstract

Diabetes is a chronic, progressive disease associated with significant morbidity and mortality. Fortunately, several long-term, prospective studies have demonstrated how proper medical management can significantly reduce the risks associated with diabetes. Based on these studies, the American Diabetes Association and American Association of Clinical Endocrinologists set forth standards and guidelines for the medical management of diabetes. The recommendations clearly outline a multifactorial plan for managing diabetes, but they do not provide specific recommendations for selection and titration of pharmacological treatment. Published reports suggest that specialists are adept at using complex drug regimens to reach the goals set forth in the guidelines, but primary care practitioners could benefit from treatment algorithms that guide the management of drug regimens for diabetes. This article briefly reviews the pharmacological management of type 2 diabetes and describes our experience developing a treatment algorithm for use within a managed care plan.

Diabetes is a chronic, progressive disease associated with significant morbidity and mortality. Patients with uncontrolled type 2 diabetes experience significant microvascular and macrovascular complications, which occur even in relatively asymptomatic individuals. With respect to microvascular complications, ~ 16–21% of patients with diabetes experience retinopathy, 12–23% nephropathy, and 20–40% neuropathy.[1] The risk of macrovascular complications, such as cardiovascular disease (CVD), cerebrovascular disease, and peripheral vascular disease, is several times higher in patients with type 2 diabetes than in nondiabetic patients.

Several landmark studies clearly document that patients who aggressively control their blood glucose levels are less likely to develop complications associated with diabetes.[2,3] Based on these studies, the American Diabetes Association (ADA)[4] and American Association of Clinical Endocrinologists (AACE)[5] set goals for the outcome of medical intervention as a hemoglobin A_{1c} (A1C) value of < 7 and 6.5%, respectively; preprandial plasma glucose levels of 90–130 mg/dl; and peak postprandial plasma glucose levels of < 180 mg/dl.[3] One of the landmark studies, the U.K. Prospective Diabetes Study,[2] conclusively demonstrated that for every percentage point decrease in A1C (e.g., from 8 to 7%), there was a 35% reduction in the risk of microvascular complications. In addition, research shows that reducing risk factors for CVD, such as diabetes, effectively prevents or slows CVD. With respect to reaching these goals, the guidelines emphasize lifestyle modifications (e.g., diet and exercise), patient education, and regular follow-up to prevent or delay complications.

Incorporating Guidelines Into a Managed Care Practice

Excellus BlueCross BlueShield is a nonprofit independent licensee of the BlueCross BlueShield Association and is New York's largest nonprofit health plan. It collectively provides health insurance to 2 million people and interacts with ~ 3,000 primary care providers in the greater New York state area. Of its 2 million members, ~ 5% have been diagnosed with diabetes.

In 1998, an Excellus BlueCross BlueShield advisory board charged a team of medical directors, nurses, pharmacists, and certified diabetes

Address correspondence:
Mona M. Chitre, PharmD, CGP, Excellus BlueCross BlueShield, 165 Court Street, Rochester, NY 14647

educators with the task of establishing a disease management program for diabetes. The purpose of the diabetes management program (DMP) was to make practices within the plan consistent with the recommendations of the ADA and the National Committee for Quality Assurance (NCQA). The resulting DMP included educational programs for practitioners, readily available practice guidelines, reports to alert practitioners to process and outcomes data, access to case management services, and access to consulting services from specialists (e.g., endocrinologists and diabetes educators). Specific examples of these activities include:

- Sending members a quarterly newsletter about the importance of follow-up (e.g., A1C and lipid profiles) and lifestyle modifications (e.g., healthy recipes and exercise tips)
- Sending members a fact sheet summarizing diabetes management guidelines and expectations
- Sending practitioners diabetes provider reports that detailed the status of their patients with respect to criteria from the practice standards, such as regular eye exams, target A1C values, and data regarding comorbidities
- Providing practitioners with financial incentives to keep their patients within the guidelines
- Encouraging practitioners to seek consultation for patients not responding to treatment or those whose diabetes is difficult to manage
- Distributing a directory of resources, which included contact information for the ADA, outpatient diabetes programs, endocrinologists, diabetes-billing help center, and case management services
- Providing free glucose meters.

In 1999, the DMP received the "Best of Blue" national award given by the BlueCross BlueShield Association for excellence and innovation. A key part of the DMP was the chance for those involved to provide feedback. A consistent message from the specialists, educators, and primary care practitioners was that the primary care practitioners clearly understood the treatment goals for diabetes, but they needed help prescribing and managing drug therapy. Furthermore, the primary care practitioners were asking for basic information on the mechanisms of action for each type of drug, treatment goals, and follow-up guidelines.

The ADA's standards allow any agent to be used for first-line treatment and do not address appropriate adjustments for patients outside their glycemic goals. Reports in the literature suggest that well-defined protocols for the use of oral agents in the management of diabetes would produce better results,[1,6–10] and the experience of our DMP concurs with these reports.

Pharmacological Intervention

In nondiabetic patients, glucose homeostasis is mediated by the stimulation of insulin secretion from the β-cells in the pancreas, which acts to suppress the endogenous hepatic production of glucose and stimulate glucose uptake in the peripheral tissues (e.g., muscle and fat). In patients with type 2 diabetes, which accounts for ~ 90–95% of the diagnosed cases of diabetes, there is some degree of resistance to insulin in the hepatic and peripheral tissues, and the β-cells have a diminished ability to secrete insulin. It is unclear which mechanism plays the dominant role in the pathology of type 2 diabetes and the associated complications.[11]

In the United States, there are five main classes of oral medications approved for the treatment of type 2 diabetes (Table 1) as monotherapy or combination therapy for patients who are not able to control their diabetes with diet and exercise alone.

Secretagogues act by increasing the secretion of insulin from the β-cells in the pancreas. The effect of higher plasma insulin concentrations suppresses hepatic glucose production and facilitates glucose uptake by the muscles.[12,13] Most patients receiving monotherapy with secretagogues will eventually require a second agent from another class because the production of insulin by β-cells eventually declines, and stimulating the β-cells no longer improves insulin secretion.

Secretagogues have a neutral or slightly beneficial effect on plasma lipid levels. The major concern is the potential for hypoglycemia and weight gain, although the nonsulfonylurea agent repaglinide is thought to have a lower incidence of hypoglycemia than the sulfonylureas.[14] Some evidence suggests that the actual incidence of hypoglycemia resulting from treatment with any agent is of minor significance in comparison with the incidence of hypoglycemia associated with lifestyle changes.[1,14] Regardless, some patients will be at higher risk than others, and the relative risk should be considered.

The biguanides act by suppressing basal hepatic glucose production and enhancing insulin uptake by the muscle. The fasting blood glucose level will begin to decrease within 3–5 days after initiating therapy, but the full effect takes 1–2 weeks. Biguanides reduce plasma triglycerides and LDL cholesterol levels. Metformin is the

Table 1. Oral Agents Approved for Treatment of Type 2 Diabetes in the United States

Class	Brand Name	Generic Name
Thiazolidinediones	Avandia	Rosiglitazone
	Actos	Pioglitazone
Biguanides	Glucophage	Metformin
α-Glucosidase inhibitors	Precose	Acarbose
	Glyset	Miglitol
Secretagogues (second-generation sulfonylureas)	Glucotrol, Glucotrol XL	Glipizide
	Micronase, DiaBeta	Glyburide
	Glynase	Glyburide
	Amaryl	Glimepiride
Sulfonylureas (first generation)	Diabinese	Chlorpropamide
Secretagogues (nonsulfonylurea)	Starlix	Nateglinide
	Prandin	Repaglinide

only agent in any of the oral antidiabetic drug classes that can reduce both microvascular and macrovascular complications when used as monotherapy for the treatment of type 2 diabetes.[2,3] Most patients treated with metformin maintain a consistent weight or lose weight. The incidence of hypoglycemia associated with metformin is rare because metformin does not increase insulin secretion. Biguanides are contraindicated in patients with renal disease or dysfunction, congestive heart failure that requires pharmacological treatment, and acute or chronic metabolic acidosis.[15]

Thiazolidinediones (TZDs) rejuvenate β-cell activity and act to improve sensitivity to insulin.[15–17] The fasting blood glucose levels begin to decrease within 5–7 days, but the maximum potential of a given dose is not reached for 3–4 weeks. TZDs when used alone or in combination with other medications for diabetes can cause fluid retention and exacerbate or lead to congestive heart failure. Liver toxicity occurs in some patients, so liver function must be monitored monthly.

α-Glucosidase inhibitors decrease postprandial glucose levels by delaying the digestion of carbohydrates and absorption of glucose. Although it does not reverse any pathophysiological defects, slowing the rate of absorption of glucose is thought to give the β-cells more time to secrete the necessary insulin. α-Glucosidase inhibitors must be taken with the first bite of food. The effect of this class of drugs on lipid profiles and body weight is neutral. The major side effects are gastrointestinal in nature.

There are a few new classes of drugs, such as synthetic amylin hormone (pramlintide) and incretin mimetics (exenatide). There are also some combination products new to the market. Because they are relatively new, they are not included in any of the algorithms published in the literature. But based on preliminary data, these injectable agents (e.g., exenatide and pramlintide) will likely be second-line therapy.[18] It is assumed that combination products are used when appropriate per an algorithm because the pharmacology suggests that combinations should be used when a patient has been stabilized on both medications individually.

Treatment Strategy

When developing a pharmacological treatment strategy for patients with type 2 diabetes, it is important to remember that glucose disposition is part of a complex metabolic and cardiovascular system that includes dyslipidemia, hypertension, obesity, and coagulability, among others morbidities.[19] The goals for A1C are general, and it is expected that goals for each patient be customized based on a complete assessment of the patient. Aggressive glycemic control is appropriate in some patients, whereas the risk of hypoglycemia, weight gain, or other complications necessitates less aggressive goals in other patients, such as those with limited life expectancy, those who are very young or old, and those with select comorbidities. In addition, the presence and severity of comorbidities vary among patients and over time within a single patient. Thus, regular reassessment is required.

Once treatment goals have been individualized, several patient-specific factors should also be considered when selecting a drug regimen. Such factors include differences in how the medications work, the potential for hypoglycemia, time to onset of action, estimated time spent outside of goals, potential compliance with the regimen, and the patient's environment (e.g., hospitalized, institutionalized, or ambulatory). Essentially, the goals and treatment regimen for a specific patient must be weighed carefully against the relative risks. The ideal treatment algorithm organizes all of the considerations reviewed herein into an evidence-based resource to supplement good clinical judgment.

Excellus BlueCross BlueShield Algorithm

Excellus BlueCross BlueShield was charged with implementing a treatment algorithm that would serve as a quick reference for primary care practitioners and a tool to augment other components of the DMP described herein. The ideal algorithm would help physicians prescribe drug therapy to get patients to goal as quickly as possible and have the best chance for maintaining patients at goal. It was also intended to guide difficult patients to specialists earlier in the process and minimize the amount of time patients spend outside of goal.

The Excellus BlueCross BlueShield algorithm was drafted by a clinical pharmacist and then reviewed by the peer review panel, which consisted of primary care physicians, endocrinologists, certified diabetes educators, and registered nurses. The approved algorithm was sent to all the primary care practitioners within the Excellus BlueCross BlueShield network.

For an algorithm to successfully influence the practice of Excellus BlueCross BlueShield physicians, it was determined that it must meet the following criteria:

- The document must be easy to use and serve as a quick reference.
- It must advocate classes of agents rather than specific products.
- It must be consistent with the pharmacology of the available agents.
- It must offer first-, second-, and third-line options, and provide follow-up guidelines.
- It must get patients to goal quickly.

Development Process

Our review of the literature identified several articles that address the available medications and suggest how they might be used. However, only two articles[17,18] proposed first-line and subsequent therapeutic options based on the pathophysiology of type 2 diabetes, available clinical trials describing the safety and efficacy of drug regimens, and pharmacology of the drugs. The algorithms shared common principles that outline a framework within which the algorithm should be used. These principles include:

- Use the algorithms to manage drug therapy in patients with diabetes that is not controlled by lifestyle modifications.
- Continue to emphasize lifestyle modifications throughout the treatment process.
- Consider insulin as a viable option each time the patient is assessed.
- Use a goal for A1C of ″ 7%.

These principles became the basis for our algorithm. However, to serve our goals, we added principles to better define the parameters of our algorithm. The principles unique to our algorithm include advocating pharmacological intervention for patients who have a fasting plasma glucose level > 200 mg/dl or have not met their glycemic goals after 3 months of

lifestyle therapy, assessing patients for insulin resistance before starting therapy, considering insulin when monotherapy is failing or A1C is > 10%, and referring patients with an A1C > 8% for 9 months to an endocrinologist. Using these principles, we set out to develop an algorithm unique to Excellus BlueCross BlueShield.

The Algorithm

The resulting algorithm (Figure 1) appeared on the front of a standard-size piece of paper, and Quick Tips were included on the back (Figure 2). Our peer review panel strongly advocated making insulin an option at any point in the process. Short-term insulin use was intended to get patients to goal quickly while waiting for an effective oral regimen to be identified. One of the big differences in our approach is that we set forth specific criteria for identifying patients who have "failed lifestyle modification" and should be started on a drug regimen (e.g., patients who are outside the target range for their A1C for 3 months or have a fasting plasma glucose level > 200 mg/dl).

We prefer first-line oral agents that minimize the degree of insulin resistance and suppress hepatic glucose production rather than increase plasma insulin concentrations. The decision to include TZDs and metformin as first-line therapy draws from the algorithm proposed by Wyne et al.[15] and direction from our peer review panel. Stimulating insulin secretion and minimizing insulin resistance both have the potential to bring a patient to goal, but it is theorized that bringing a patient to goal by reducing insulin resistance is more likely to reduce the risk of macrovascular complications.[12] The arguments for and against these data are much more detailed than described here, but this is the essence of using biguanides and TZDs before secretagogues and α-glucosidase inhibitors. These are not wholly evidence-based claims.

Two case studies from actual Excellus BlueCross BlueShield members illustrate how the algorithm is used to guide practitioners.

Case Study 1

M.S. is a 67-year-old woman who went to her primary care physician with a complaint of fatigue. She is 5'5" tall and weighs 200 lb. A fingerstick blood glucose test showed a nonfasting blood glucose of 240 mg/dl. M.S. was sent to the laboratory the next day for a fasting blood glucose and an A1C measurement. Her fasting blood glucose was 175 mg/dl, and her A1C was 10.2%. M.S. was diagnosed with type 2 diabetes and scheduled for diabetes education. Her physician started her on insulin glargine at bedtime and a rapid-acting insulin analog for coverage of her meals based on carbohydrate content. She was scheduled for follow-up education and a laboratory visit in 3 months.

Per the algorithm, lifestyle modification is first-line intervention and

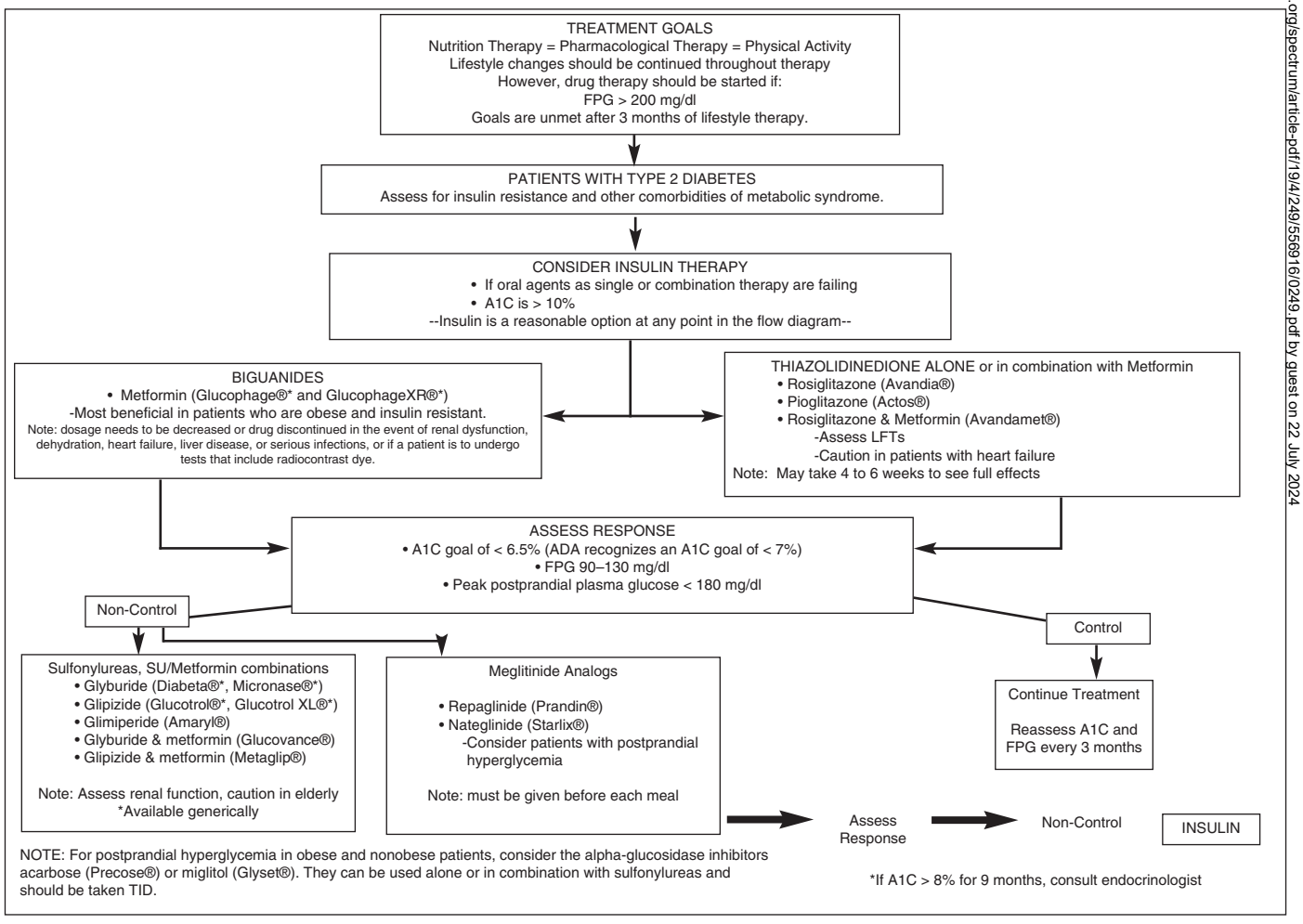

Figure 1. Excellus algorithm. FPG, fasting plasma glucose; LFT, liver function test; SU, sulfonylurea.

Diabetes is a chronic illness that requires continual medical care and education to prevent complications.

- Patient and family education is an essential element in treating each individual patient. Recognition that each patient may have individual medical and psychosocial needs is critical.

DIABETES CONTROL GOALS*

Goals	Endpoints	Assessment
Glycemic control	A1C goal of < 6.5% (The American Diabetes Association recognizes an A1C goal of < 7.0%)	Measure every 3 months
Blood pressure control	< 130/80 mmHg	Every visit
Lipid control	LDL < 70 mg/dl† Triglycerides < 150 mg/dl HDL > 45 mg/dl	Measure yearly or more frequently if goals are not met
Urine protein measurement	Microalbuminuria (< 30 mg/24 hours)	Measure yearly

*American Diabetes Association Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 26 (Suppl.):S33–S50, 2003.
†National Cholesterol Education Program: Implications of clinical trials for the ATP III guidelines. *Circulation* 110:227–239, 2004

Diabetes Patient Care:

At each visit, the provider may want to:
- Review the patient's self-monitoring glucose log
- Assess weight
- Examine feet visually
- Stress smoking cessation if the patient is a smoker
- Assess psychosocial impact of diabetes (high incidence of comorbid depression)

Periodically remind patient regarding:
- Yearly dental inspection
- Yearly eye exam
- Lifelong diabetes self-management skills
- Yearly flu shot
- Pneumococcal vaccination

PHARMACOLOGIC THERAPY
This is a complete listing of medications as of 11/04

Therapeutic Class	Drug Names	Increases Peripheral Glucose Uptake	Decreases Hepatic Glucose Secretion	Increases Insulin Secretion	Delays Carbohydrate Absorption	Target Organ Sites
Biguanide	Glucophage* Glucophage XR*	X	X			Liver and intestine
Thiazolidinediones	Avandia Actos	X	X			Muscle, adipose tissue, and liver
α-glucosidase inhibtors	Precose Glyset				X	GI tract
Sulfonylureas (second-generation)	DiaBeta* Micronase* Glynase* Glucotrol* Glucotrol XL* Amaryl	X	X	X		Islet cells of pancreas
Meglitinide analogs	Prandin Starlix			X		Islet cells of pancreas

*Generic available

Figure 2. Quick Tips included on back page of the Excellus BlueCross BlueShield type 2 diabetes treatment algorithm. GI, gastrointestinal.

remains a key management tactic. The algorithm also calls for M.S.'s physician to consider insulin therapy because of her A1C > 10%. M.S. was not assessed for insulin resistance or metabolic syndrome at her physician's discretion.

On follow-up, lifestyle modifications secondary to education were helping, and her A1C value had decreased to 8.7%. M.S. had become comfortable with lifestyle changes and insulin use. Her primary care provider decided to follow her for 6 weeks before making adjustments to her therapy.

In the past, this primary care practitioner routinely, regardless of A1C, started all patients on a sulfonylurea for 3–6 months and then added a biguanide if necessary. Lifestyle education consisted of pamplets and brochures. After the algorithm was distributed, he changed his practice and now varies his approach to pharmacological management and patient education. M.S.'s case shows how the algorithm could be used for newly diagnosed patients, but some patients enter the algorithm after first-line assessment, as described below.

Case Study 2

M.J. is a 53-year-old man who has been living with type 2 diabetes for 10 years. He is currently on a regimen consisting of a biguanide and a TZD. Initially, he had good blood glucose control, with fasting plasma glucose levels between 90 and 120 mg/dl. His A1C has ranged from 6.2 to 7.0%. At M.J.'s visit 3 months ago, his A1C was 8.0%.

Per the algorithm, it would be appropriate to stress lifestyle therapy and consider dosage adjustments or the addition of a third pharmacological agent. The best course of action is based on clinical judgment. Considerations include the potential for M.J. to tolerate higher doses of his biguanide and TZD, results of liver function tests, assessment of compliance, willingness to self-administer injectable agents (e.g., insulin), and the appropriateness of a third agent.

M.J.'s physician requested a nutritional consultation; ran standard laboratory tests, including a lipid panel, liver function tests, and A1C; and asked M.J. to continue to monitor his blood glucose at home. At the follow-up visit, M.J.'s A1C increased again to 8.2%, and his blood glucose readings were between 110 and 180 mg/dl. His other laboratory values were similar to baseline, with mild increases in LDL cholesterol. At follow-up, M.J. admitted to noncompliance with his biguanide because of gastrointestinal discomfort. His physician decided that M.J. has had further β-cell destruction and that the best course of therapy would be to start him on insulin glargine at bedtime and continue his TZD. He will monitor M.J. and follow up in 3 months.

M.J.'s primary care practitioner took an aggressive but appropriate approach to gain control of M.J.'s glucose. The dose of the TZD was previously optimized. Clinical judgment led the practitioner away from a secretagogue. α-Glucosidase inhibitors had low potential for success in this patient because fasting blood glucose values suggested that his glucose was inconsistent throughout the day rather than just postprandially. In addition, this patient was unlikely to tolerate gastrointestional side effects. Exenatide was another reasonable option. Pramlintide was not an option because the patient just started using insulin. Neither of these agents is included in the current version of the algorithm, but if they were, our expert panel considers exenatide to be a reasonable option, whereas pramlintide would be reserved for patients already receiving appropriate doses of insulin.

Review of Excellus BlueCross BlueShield Algorithm

In an ideal situation, we would have prospectively measured the impact of the algorithm on pharmacological intervention in our patient population. But given the number of programs working to improve the care of our patients, it was impossible to attribute outcomes to a specific intervention, such as our algorithm. Nonscientific assessment of the algorithm indicates that the practitioners, which include primary care practitioners, nurses, and ancillary office staff, appreciate the resource and use it regularly. Surprisingly, we did not receive any negative comments. In fact, the algorithm was eventually made available to retail pharmacies. The second page of the algorithm has since been referred to as a "patient bill of rights" and used to get patients involved in their follow-up and goals. Since putting the algorithm to use, we have decided to add exenatide and pramlintide as second-line therapy options and will distribute an updated version of the algorithm in the future.

Conclusions

Without prospective clinical trials that test algorithms in clinical practice, we cannot firmly advocate one algorithm over another for all practice settings. Ideally, the results of studies investigating the role of insulin resistance in diabetes-associated complications and long-term outcomes will provide more useful evidence to define the role of specific drug regimens. However, even with such evidence, a variety of algorithms will be required to meet the needs of various practice settings.[4]

We showed how the principles outlined here could be used to design an algorithm for a managed care practice. The flow of an algorithm should be structured to so that it helps identify when patients should begin drug therapy, guide practitioners toward an appropriate regimen, outline follow-up plans, and allow patients to gain and maintain glycemic control in a timely manner without complications.

Given the complexity of the pharmaceutical management of diabetes and the trend for patients to be managed primarily by general practitioners, algorithms are a useful way to improve the quality of drug regimens for the management of diabetes.[1,7,8,19] Our DMP discovered that primary care practitioners wanted help with prescribing and titrating oral drug regimens for the treatment of diabetes, and they subsequently welcomed and appreciated the algorithm we developed.

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Mona Chitre, PharmD, CGP, is director of clinical services with FLRx Pharmacy Management, the Pharmacy Management Division of Excellus BlueCross BlueShield, and Susan Burke, RN, BSN, CDE, is manager of new product development and quality management at Excellus BlueCross BlueShield in Rochester, N.Y.