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Diabetes: New oral medications, new attitudes

In 1998, we celebrated the 75th anniversary of the presentation of the Nobel Prize in Medicine to Dr. Frederick Banting and Professor J.R.R. Macleod for their discovery of insulin. They, along with Professor J.C. Collip and Charles Best, then a medical student, treated their first diabetic patient, a 14-year-old boy weighing 64 pounds, in January of 1922.¹ Continuing on insulin therapy, the young man went on to gain weight, recover, and live until the age of 27, when he died of pneumonia. Prior to that time, the diagnosis of diabetes was an automatic death sentence, so that the prolongation of life and the possibility of pregnancy and childbirth in diabetic women seemed miraculous.

The vision of a disease conquered began to fade as diabetic patients lived longer, but developed complications like blindness, end-stage kidney disease, neuropathies and early atherosclerosis. Insulin treatment had transformed diabetes from an acute illness to a chronic illness that gradually produced life-disrupting long-term debility (see Table 1).

Clinical studies

Practitioners through the years have considered the most probable cause of long-term problems to be prolonged hyperglycemia and have debated whether improved glycemic control could lead to improved outcomes. The debate was difficult to resolve while glucose testing was done with urine, because until home blood glucose monitoring became available in the late 1970s, tight control of blood glucose could not be attempted without risking hypoglycemic episodes.³ Nonetheless, the first large-scale trial to examine the importance of glycemic control in Type 2 diabetes patients, the University Group Diabetes Program (UGDP), was completed by 1970.⁴ Five treatment arms compared diet plus placebo to standard and variable insulin doses and to two oral medications, tolbutamide (Orinase®) and the biguanide phenformin, later removed from the US market. Although glucose control was better in the insulin group where doses were titrated according to fasting glucose levels, no treatment group had a clear advantage in microvascular or cardiovascular outcomes. After a mean follow-up of 5.5 years, the trial was prematurely terminated because of unexpected excess cardiovascular mortality in the tolbutamide group.^{5,6} Two implications followed from UGPD: that improved glucose control alone did not improve health,

Table 1.

Clinical Complications of Type 1 Diabetes²

Complication	Cumulative Prevalence in Patients (%)
Visual impairment	14
Blindness	16
Renal failure	35
Amputation	12
Stroke	10
Myocardial infarction	25

and there was a possibility that sulfonylureas produced direct cardiovascular damage. As a consequence, practitioners had no good evidence for many years that strict glucose control was clinically beneficial, and patients were not encouraged to work toward well-defined metabolic goals.

Evidence that intensive therapy does improve health finally came from the DCCT, the Diabetes Control and Complications Trial.⁷ Beginning in 1983, almost 1500 Type 1 diabetes patients between the ages of 13 and 39 were recruited and followed for an average of 6.5 years. Two cohorts were studied: patients with early disease and no retinopathy, and those with the disease for 1 to 15 years with mild-to-moderate retinopathy. Patients were randomized to conventional twice-daily insulin injections versus three or more daily injections or insulin administered by pump, with glucose monitoring at least four times daily. Intensive therapy lowered hemoglobin A_{1c} to 7%, compared to 9% in the conventional groups. In the first group with early disease, the risk of retinopathy was decreased by 76% by intensive treatment, and in the second group, the progression of retinopathy was decreased by 54%. In addition, the incidence of nephropathy and neuropathy was much lower in the intensive treatment groups (see Table 2).

Because Type 2 patients develop the same complications and disabilities, it is logical to believe that improved glucose control in Type 2 patients would also produce similar benefits.

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Table 2.
Decrease In Diabetic Complications with
Intensive Therapy in DCCT⁷

Complication	Reduction in Incidence (%)
Retinopathy	
Cumulative incidence (early disease)	76
Sustained progression (later disease)	54
Severe or proliferative	47
Laser treatment	56
Nephropathy	
Microalbuminuria	39
Proteinuria	54
Neuropathy	60

Confirmation of this hypothesis first came from a six-year study at Kumamoto University of 110 Japanese patients with Type 2 diabetes.⁸ In a trial design based on DCCT, two groups of subjects, those with no retinopathy or microalbuminuria and those with discernible retinopathy and urinary albumin less than 30 mg/24 hours, were randomized to conventional twice daily insulin vs multiple daily injections with the goal of normalizing glucose levels throughout each day. At the baseline, patients with an average age of 50, already on twice-daily intermediate-acting insulin, had hemoglobin A_{1c} values hovering around 9.0. Those who continued on conventional therapy maintained a hemoglobin A_{1c} of 9.4 during the study, compared to 7.1 for the patients in the intensively-treated groups. As in the DCCT, intensive therapy decreased the incidence and progression of retinopathy, nephropathy and neuropathy. From the study results, the authors defined appropriate metabolic goals as hemoglobin A_{1c} less than 6.5%, fasting blood glucose below 110 mg/dl and two-hour postprandial blood glucose below 180 mg/dl. Patients within these parameters showed no microvascular disease progression.

Meanwhile, a much larger multi-center study was in progress in Great Britain. The UKPDS, the United Kingdom Prospective Diabetes Study, began recruiting patients in 1977 to find out if tight glucose control in Type 2 patients over a protracted observation period could lead to better long-term outcomes.⁹ Between 1977 and 1991, over 5000 newly-diagnosed patients, with an average age of 54 years, entered the study. They were randomized to intensive vs conventional management, defined by glycemic goals of maintaining fasting blood sugar below 6 mmol/L (107 mg/dl) or below 15 mmol/L (270 mg/dl) respectively. Conventional patients all began with diet therapy, while the intensively treated patients were randomized to therapy with insulin or oral sulfonylureas (chlorpropamide or glyburide, or later, glipizide).

If patients in either group at regular check-ups exceeded glycemic targets, they received stepped therapy until goals were attained. Those on diet alone were randomized to insulin, sulfonylureas, or if markedly overweight, to metformin. Those already on sulfonylureas added metformin or insulin, and those on insulin titrated their dosage to goals. Median daily insulin doses at 3, 6, 9, and 12 years in fact increased from 22 units up through 28, 34, and 36 units. Earlier publications from the UKPDS study had documented that in Type 2 patients, after diagnosis, pancreatic beta-cell function declines over the years, so that patients can expect periodic revisions in their therapy.⁹ Conventionally managed patients in the study maintained a hemoglobin A_{1c} of 7.9%, while intensively managed patients lowered theirs to 7.0%.

Because hypertension is commonly associated with Type 2 diabetes, a hypertension study was embedded into the ongoing glucose control study beginning in 1987.^{11,12} Over 1100 hypertensive patients already enrolled in UKPDS were randomly assigned to antihypertensive drug treatment with atenolol or captopril vs less strict blood pressure control without the help of either beta-blockers or ACE inhibitors. In the tight management group, target blood pressure was less than 150/85 mm Hg, and other agents were added if captopril 50 mg po twice daily (BID) or atenolol 100 mg po daily (QD) proved to be insufficient.

Unlike DCCT, which focused on microvascular complications, UKPDS also set out to look at macrovascular consequences like atherosclerosis and true end-points like cardiovascular death.⁹ After statistical analysis of the study groups, made even more complex by therapeutic overlap between groups, the investigators concluded that the intensively treated patients stayed well longer. Microvascular end-points were reduced 25%, any diabetes-related end-point was reduced by 12%, diabetes-related death by 10%, and all-cause mortality by 6%. The risk of macrovascular death was not reduced. Weight gain at the ten-year point was 3 kg for conventional patients and 6 kg for intensively treated patients. Those on insulin gained 7 kg. Neither insulin nor sulfonylureas increased cardiovascular mortality (see Table 3).

In the nested study where tight blood pressure management was studied in the UKPDS patients, patients on atenolol or captopril achieved a mean blood pressure of 144/82 mm Hg compared to 154/87 mm Hg in the controls.^{11,12} The reduction in blood pressure was accompanied by a reduced risk of complications and death due to diabetes. The risk reduction was 37% in microvascular end-points, 24% in diabetes-related end-points, 32% in diabetes-related death, with a non-significant reduction in all-cause mortality. Strokes declined by a remarkable 44% and risk of heart failure dropped by 56%. There was also a 34% decrease in two-step progression of retinopathy and a 47% reduced risk of visual loss (see Table 3).

Treatment of hyperglycemia alone may not reverse all disease complications. This study illustrates the importance of direct treatment of hypertension in addition. Similarly, aggressive treatment of hyperlipidemias will probably result in better long-term health in Type 2 patients.

Guidelines

Ever since DCCT, both patients and practitioners have used the evidence from the trial to regain control of disease management. Increasingly, every treatable complication has generated a management goal. Diabetes educators have encouraged patients not only to carry out beneficial lifestyle changes, but

to take ownership of their own treatment programs. Table 4 presents a listing of major diabetic complications and their related disabilities, with selected monitoring parameters.

In our own state, where over 300,000 people have diabetes, the Wisconsin Diabetes Advisory Group has published the Essential Diabetes Mellitus Care Guidelines, based on American Diabetes Association Guidelines and incorporating regional consensus.¹³ The guidelines with supporting documents and references may be found on the Internet at <http://www.dhfs.state.wi.us/health/index.htm>. A wallet card version is also available for patients through the Wisconsin Diabetes Control Program at 608-261-6871. See next page.

Table 3.

Diabetes Complications in Type 2 Patients Treated Intensively vs Conventionally in UKPDS^{9,11}

Endpoint	Risk Reduction with Intensive Blood Glucose Control (%) (UKPDS 33)	Risk Reduction with Intensive Hypertension Control (%) (UKPDS 38)
Any Diabetes-Related Endpoint	12	24
Diabetes-Related Death	10	32
All-Cause Mortality	6	18 (not significant)
Microvascular Endpoints	25	37
Macrovascular Endpoints	No reduction	34
Stroke	+7	44
Heart Failure	9	56

Table 4.

Management of Diabetes Complications

Complication	Care and Monitoring Parameters	Complication-Related Disabilities
Hyperglycemia	Blood glucose Hemoglobin A _{1c} Diet, Exercise, Medication Self-Management Training Dental Exams	Myocardial Infarct Stroke Renal Failure Peripheral Vascular Disease Vision Problems Periodontal Disease
Hypertension	Blood Pressure Renal Function Tests Urinalysis	Myocardial Infarct Stroke Renal Failure
Hyperlipidemia	Lipid Panels	Myocardial Infarct Stroke Peripheral Vascular Disease
Retinopathy	Eye exams	Visual Impairment Blindness
Neuropathy	Foot and Skin Care	Peripheral Vascular Disease Non-Healing Tissue Ulcers Amputation Gastroparesis Impotence

Medications

Since 1994, there has been an explosion of new oral medications in four new therapeutic categories for Type 2 diabetes in the U.S.¹⁴ In addition to sulfonylurea hypoglycemics, we now have a non-sulfonylurea hypoglycemic, repaglinide (Prandin®), two alpha-glucosidase inhibitors (GSIs), acarbose (Precose®) and miglitol (Glyset®), a biguanide, metformin (Glucophage®), and the first thiazolidinedione (TZD), troglitazone (Rezulin®).¹⁵ In addition, insulin lispro (Humalog®), a new rapid-acting, recombinant insulin analog with a short duration has been introduced. It can be injected immediately prior to meals and is physically compatible with isophane (NPH) and extended zinc (ultralente) insulins.

The new classes of agents have different sites of action so that they can function not only as alternatives to sulfonylureas, but in combination with each other to delay the need for insulin therapy in Type 2 patients. Because the GSIs, metformin, and troglitazone do not stimulate

Essential Diabetes Mellitus Care Guidelines - Wisconsin

*Care is a partnership between the patient, family and the diabetes team:
the primary care provider, diabetes educator, nurse, dietitian, pharmacist and other specialists.*

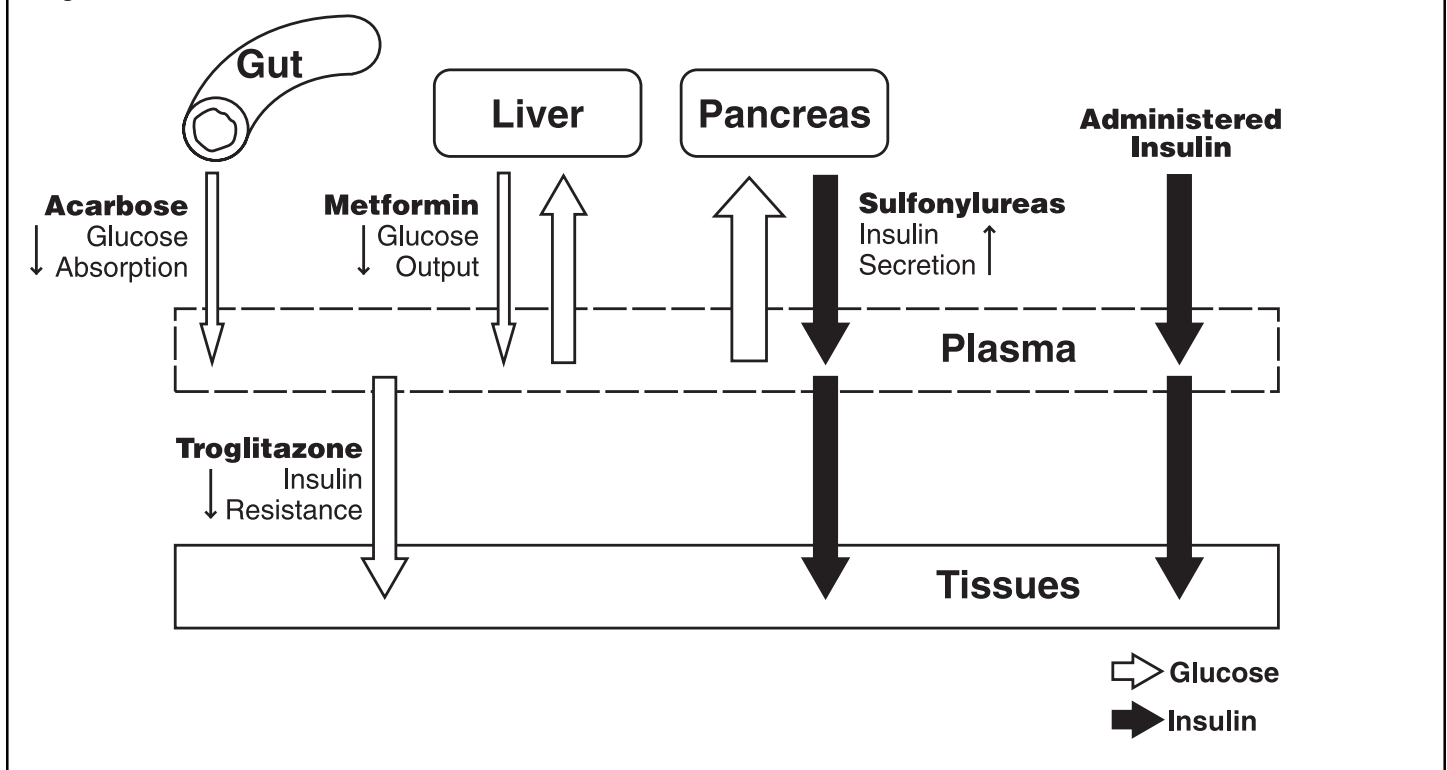
Abnormal physical or lab findings should result in appropriate interventions.

For particular details and references for each specific area, please refer to the companion supporting documents.*

Concerns	Care/ Test	Frequency
General Recommendations	<ul style="list-style-type: none"> Diabetes focused visit Review management plan, problems and goals on control and complications 	<p><i>Type 1*</i>: every 3 months <i>Type 2*</i>: every 3 - 6 months or more often based Each focused visit; revise as needed</p>
Glycemic Control	<ul style="list-style-type: none"> Review meds and frequency of low blood sugar Self blood glucose monitoring, set & review goals HbA1C - Goal: < 7.0% or <= 1% above lab norms ... If HbA1c > 8.0%, action is recommended Weight/BMI/Growth 	<p>Each focused visit 2 - 4 times/day or as recommended Every 3 - 6 months Each focused visit</p>
Kidney Function	<ul style="list-style-type: none"> Urinalysis Urine for microalbuminuria: If higher than 30 mcg/mg creatinine or >30 mg/24 hours, initiate ACE inhibitor (unless contraindicated) Creatinine clearance & protein..... 	<p>At diagnosis and yearly <i>Type 1</i>: Begin with puberty or after 5 years duration, then yearly <i>Type 2</i>: At diagnosis, then yearly Yearly, after microalbuminuria > 300mg/24 hour</p>
Cardiovascular	<ul style="list-style-type: none"> Smoking Lipid profile Adult goals: Triglycerides < 200 mg/dL HDL > 35 mg/dL LDL < 100 mg/dL (optimal goal) Blood pressure Adult goal: < 130/85 Children's goal: below 90% of ideal for age Aspirin prophylaxis (unless contraindicated)..... Exercise/Diet/Weight Goals 	<p>Counsel to stop every visit <i>Children</i>: If > 2 years, after diagnosis & once glycemic control is established - repeat yearly if abnormal. Follow National Cholesterol Education Program (NCEP) guidelines. <i>Adults</i>: yearly. If abnormal, follow NCEP guidelines. Each focused visit Age > 40 years Each focused visit</p>
Eye Care	<ul style="list-style-type: none"> Dilated eye exam by ophthalmologist or optometrist 	<p><i>Type 1</i>: After 5 years duration; then yearly <i>Type 2</i>: At diagnosis, then yearly</p>
Foot Care	<ul style="list-style-type: none"> Inspect feet, with shoes and socks off Comprehensive lower extremity sensory exam 	<p>Each focused visit: stress need for daily self-exam Yearly</p>
Pregnancy	<ul style="list-style-type: none"> Assess contraception/discuss family planning Preconception consult Management 	<p>At diagnosis and yearly during childbearing years 3 - 4 months prior to conception <i>Some medications (eg, oral antidiabetic agents, ACE inhibitors, angiotensin II blockers, etc.) are contraindicated during pregnancy</i></p>
Self-Management Training	<p>By diabetes educator</p> <ul style="list-style-type: none"> Curriculum to include the 15 key areas of the national standards for diabetes self-management education 	<p>At diagnosis, then every 6 - 12 months or more as indicated by the patient's status</p>
Nutrition Therapy	<p>By a dietitian</p> <ul style="list-style-type: none"> To include areas defined by the American Dietetic Association's Nutrition Practice Guidelines 	<p>At diagnosis; then <i>Type 1*</i> if age < 18 years, every 3 - 6 months or if age > 18 years, every 6 - 12 months <i>Type 2*</i> every 6 - 12 months; * or as indicated by the patient's status.</p>
Immunizations	<ul style="list-style-type: none"> Influenza vaccine Pneumococcal vaccine 	<p>Yearly for adults and children > 6 months Once for adults and children > 2 years</p>

* The entire guideline package, including supporting documents, references, quality improvement guidelines, and tools, is available at <http://www.dhfs.state.wi.us/health/index.htm> or through the Wisconsin Diabetes Control Program, 608-261-6871.

Figure 1. Sites of Action of Diabetes Medication



insulin secretion, they have a lower potential for causing hypoglycemia. They are effective only in the presence of insulin, in patients with some beta-cell function. With these agents, weight gain, and possibly hyperlipidemia and hypertension, are less likely. Long-term use of metformin causes minimal weight gain, even in overweight patients.¹⁶ In contrast, the UKPDS patients using insulin gained 15 pounds during the course of the study.⁹

Figure 1 illustrates the sites of action of currently available antidiabetic agents.

Repaglinide (Prandin®)

Repaglinide is a meglitinide, the non-sulfonyl part of the glyburide molecule.¹⁵ It stimulates insulin production in pancreatic beta cells at higher plasma glucose levels, like the sulfonylureas. It is rapidly acting and is cleared quickly by hepatic metabolism to inactive metabolites. When it is given 15 minutes prior to meals, one-hour postprandial glucose levels are lowered, although fasting glucose may not change significantly. It is indicated for treatment of Type 2 diabetes in patients whose glucose is not well controlled by diet and exercise. If its effect is inadequate as monotherapy, repaglinide may be combined with metformin. For dosing, administration, and monitoring information, see Table 5. Its most troublesome adverse effect is hypoglycemia.

Acarbose (Precose®)

Acarbose was the first alpha-glucosidase inhibitor (GSI) to

be approved in the US.¹⁵ The GSIs are competitive inhibitors of intestinal alpha-glucosidases, enzymes that hydrolyze sucrose and dietary starches into absorbable subunits. Inhibition of enzyme action significantly slows intestinal carbohydrate absorption and decreases postprandial plasma glucose peaks. The GSIs do not affect lactose metabolism. Acarbose as monotherapy usually has only a modest effect on hemoglobin A_{1c}, but can increase the hypoglycemic effects of sulfonylureas or insulin. Initial dosage is 25 mg TID (three times daily) with meals, with gradual increases to minimize adverse effects like flatulence, abdominal discomfort, and diarrhea. As dosage is gradually increased, periodic assessment of one-hour postprandial glucose can be used as a dosage guide. Acarbose may be combined with any of the other oral agents. In one recent study, 90 Chinese Type 2 patients whose blood sugar was inadequately controlled on maximal doses of sulfonylureas plus metformin were treated with acarbose 100 mg TID for 24 weeks.¹⁷ Compared to placebo, acarbose produced significantly greater reductions in postprandial glucose, hemoglobin A_{1c}, and body weight in this group, when added to the other two agents.

The nuisance side effects of acarbose abate over time. Dose-related elevations of alanine amino transferase (ALT) and aspartate amino transferase (AST) have occurred in some patients, most frequently at doses greater than 100 mg TID. Laboratory abnormalities have usually been asymptomatic and reversible on drug discontinuation, but the manufacturer

Table 5.
New Oral Diabetes Medications

Drug	Dose	Dose in Renal Dysfunction	Administration	Pregnancy Risk Factor	Monitor	Most Common Drug Combos
Repaglinide (Prandin®)	0.5-2mg TID-QID Max QD 16 mg	Use caution in changing doses	15 min prior to meals	C	FBG HGBA _{1c} Adjust Q 7 days	Metformin
Acarbose (Precose®)	25mg TID to 50 TID if <60kg 100TID >60kg	Not in patients with CrCl <25 or creatinine >2	Take with the first bite of the meal	B	Periodic 1-hr postprandial glucose; ALT, AST Adjust Q 4-8 weeks	Sulfonylureas Insulin
Miglitol (Glyset®)	25mg TID to 50-100 TID	Not in patients with creatinine >2	Take with the first bite of the meal	B	HGBA _{1c} Q 3 mo Adjust Q 4-8 weeks	Sulfonylureas Insulin
Metformin (Glucophage®)	500mg BID-TID; 850mg BID-TID Max QD 2500mg	Not in patients with creatinine >1.4 (female) or >1.5 (male) or liver problems	With meals	B	FBG HGBA _{1c} Q 3mo Renal Function Adjust Q 7-14 days	Sulfonylureas
Troglitazone (Rezulin®)	400mg QD up to 600mg; in combos, 200mg QD	No change	With meals	B	FBG HGBA _{1c} Q 3mo ALT, AST Adjust Q 4 weeks	Insulin Sulfonylureas

FBG = Fasting blood glucose HGBA_{1c} = Hemoglobin A_{1c} CrCl = creatinine clearance

recommends that transaminases be checked every 3 months during the first year of therapy and periodically after that.

Miglitol (Glyset®)

Miglitol, a second GSI, was approved by the FDA in 1997.¹⁵ It is structurally unrelated to acarbose. Like acarbose, miglitol produces smaller decreases in hemoglobin A_{1c} than glyburide, but studies typically have shown less weight gain and hypoglycemia in patients than with sulfonamides.¹⁸ It can also be used in stepwise combinations with other agents when glucose control deteriorates, to enable patients to delay insulin therapy. Also, like acarbose, miglitol is associated with nuisance gastrointestinal effects early in therapy, probably due to gas formed by bacterial fermentation of increased quantities of carbohydrate in the intestine. Unlike acarbose, it does not produce elevations of liver enzymes.¹⁵

Metformin (Glucophage®)

Metformin, approved by the FDA in late 1994, is a biguanide.¹⁵ In 1977, the first biguanide used in the US, phenformin, was withdrawn from the US market because of reports

of fatal lactic acidosis.¹⁴ Metformin has a much improved safety profile, but still can cause lactic acidosis in patients with renal dysfunction.

The biguanides lower plasma glucose by decreasing inappropriately high glucose output by the liver.¹⁵ They also improve peripheral utilization of glucose. Metformin has effectively reduced both fasting and postprandial glucose levels when used as a single agent, and has been combined successfully with other agents like sulfonylureas. The UKPDS 34 has reported spectacular results in long-term studies of obese (>120% of ideal body weight) patients placed on metformin as initial therapy.¹⁶ Newly diagnosed patients allocated to intensive metformin therapy had risk reductions of 32% for any diabetes-related endpoint, 42% for diabetes-related death, and 36% for all-cause mortality. There was little long-term weight gain. Although the authors endorsed its use as first-line therapy, caution should be used in basing recommendations on any one study.

Early adverse effects can include nausea, anorexia, metallic taste, flatulence, and diarrhea, but these problems usually

Table 6.
Oral Medications Used in Type 2 Diabetes

Drug Class	Drug	Mechanism of Action	Advantage	Adverse Effects Disadvantages
<u>Sulfonylureas</u> First generation	Acetohexamide (<i>Dymelor</i> ®) Chlorpropamide (<i>Diabinese</i> ®) Tolazamide (<i>Tolinase</i> ®) Tolbutamide (<i>Orinase</i> ®)	stimulates increase in insulin secretion by beta cells	↓HbA _{1c} 1.5-2% least expensive	hypoglycemia; drug interactions; gradual loss of glucose control; weight gain
Second generation	Glyburide (<i>Micronase</i> ®, <i>DiaBeta</i> ®, <i>Glynase</i> ®) Glipizide (<i>Glucotrol</i> ®) Glimepiride (<i>Amaryl</i> ®)	stimulates increase in insulin secretion by beta cells	similar to first-generation	same as first-generation
<u>Non-sulfonylurea Hypoglycemic</u>	Repaglinide (<i>Prandin</i> ®)	stimulates increase in insulin secretion by beta cells	short-acting, taken with meals; may be combined with metformin	hypoglycemia
<u>α-Glucosidase Inhibitors</u>	Acarbose (<i>Precose</i> ®) Miglitol (<i>Glyset</i> ®)	decreases postprandial rate of carbohydrate absorption	may be combined with other oral agents; no hypoglycemia	modest effect; intestinal gas
<u>Biguanide</u>	Metformin (<i>Glucophage</i> ®)	decreases glucose output from the liver	may be combined with other agents; no weight gain; no hypoglycemia	diarrhea; rarely lactic acidosis; (contraindicated in renal dysfunction)
<u>Thiazolidinedione</u>	Troglitazone (<i>Rezulin</i> ®)	decreases insulin resistance	may be used with insulin or oral agents; no hypoglycemia	rarely, serious liver injury; ineffective if no insulin

resolve with continued use.¹⁵ Vitamin B₁₂ supplementation may be necessary. Lactic acidosis occurs very rarely, but patients who develop any conditions that can predispose to lactic acidosis should be taken off metformin.¹⁴ These conditions include renal dysfunction or rapid decline in renal function, congestive heart failure, hypoxia, or liver impairment, since lactic acid is cleared by the liver. Metformin should be discontinued for 48 hours after administration of contrast media and not restarted until baseline renal function has been regained. Preventive discontinuation of the medication is doubly important because the symptoms of lactic acidosis like anorexia, nausea, drowsiness and fatigue, are non-specific and occur in elderly people for more benign reasons. Once the initial GI discomfort is over, gastrointestinal symptoms due to metformin are very rare, so that nausea or vomiting should be an alarm signal in a patient taking metformin. Metformin may not be advisable in patient populations like prisoners, where such symptoms could escape notice until the patient became critically ill.

Troglitazone (Rezulin®)

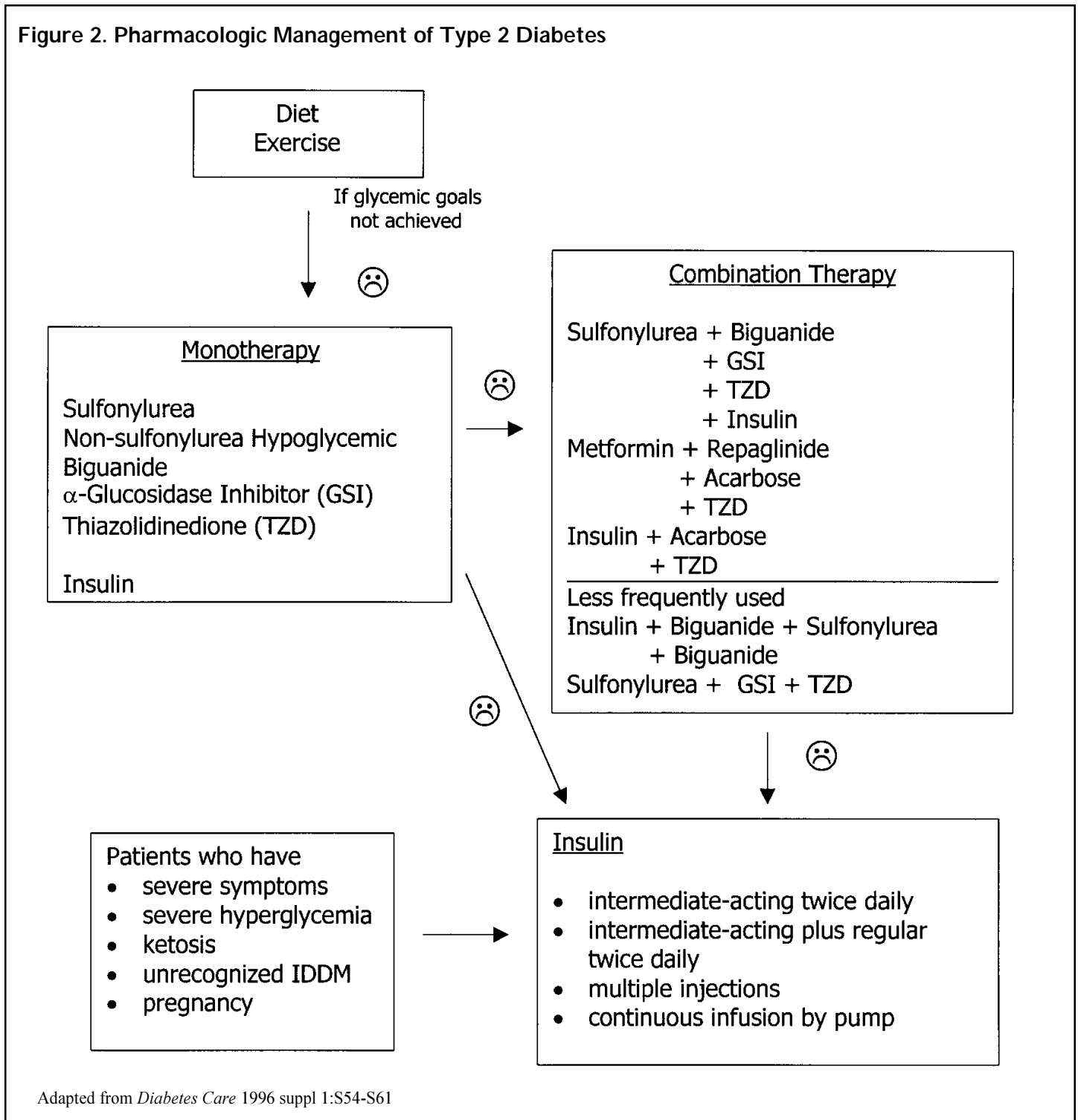
Type 2 diabetes is characterized by two primary metabolic defects: insulin deficiency and insulin resistance.² Insulin resistance precedes the development of hyperglycemia in Type 2 patients. Normally, most plasma glucose is transported

into muscle and adipose tissue, but insulin resistance prevents normal uptake. Consequently, absorption of glucose from the intestine into plasma after meals can cause prolonged elevation of glucose levels. Increased insulin production can compensate for insulin resistance unless pancreatic beta cells become fatigued and pancreatic insulin output decreases.

Troglitazone, the first thiazolidinedione, decreases insulin resistance and improves glucose uptake in peripheral tissues, particularly muscle and adipose tissues.¹⁵ Originally approved for use in Type 2 patients already taking insulin, the addition of troglitazone permits reduction in administered insulin doses. Troglitazone has also been approved for use as monotherapy, and can be used in conjunction with other oral agents. Trials are also in progress to determine if it can delay the development of Type 2 diabetes in patients at risk.¹⁹

Troglitazone is remarkably free of nuisance side effects.¹⁵ Now that it has been so widely prescribed, especially in Japan and the United States after its approval here in 1997, a very rare but sometimes fatal adverse reaction has been reported. Hepatocellular injury has resulted in scattered cases of liver failure requiring liver transplant or resulting in death.²⁰ As a result, the prescribing information now recommends checking transaminase levels at the time therapy is begun, every month for eight months, every two months at months 10 and 12, and then

Figure 2. Pharmacologic Management of Type 2 Diabetes



Adapted from *Diabetes Care* 1996 suppl 1:S54-S61

periodically. If levels are more than three times the upper limit of normal, or the patient has jaundice, troglitazone should be discontinued. The major disadvantage of the drug is its cost. The average wholesale price (AWP) for a 30-day supply ranges from \$89 to \$179 in 1998.²¹

Pharmacologic Management of Type 2 Diabetes

The American Diabetes Association has periodically updated guidelines for therapy of Type 2 diabetes²² (see Table 6 and Figure 2). Although initial therapy is diet and exercise, with the exceptions noted in the diagram, only about 10% of Type 2 patients achieve acceptable long-term glucose control without

medication.²³

Now that sulfonylureas are not the only first-line oral medications, the patient in consultation with his care team, including the physician, the nurse-educator, the pharmacist, and the dietitian, has wider choices. Because the most important element in diabetes management is self-care, and informed, motivated patients can manage glucose control more effectively, patient choice is an important consideration. The older sulfonylureas address the immediate problem of insulin deficiency and are the least expensive choice. They differ from the second-generation sulfonylureas mainly in kinetic profiles, while safety and efficacy are comparable.⁹ For patients unlikely to manage possible hypoglycemic events, metformin, acarbose, miglitol or troglitazone are all useful. If glycemic control is not satisfactory with monotherapy at optimal dosing, other oral agents can be added in stepwise combinations, as indicated in Figure 2. Combinations of oral agents with insulin usually are used later in the course of therapy.

Because Type 2 diabetes is an evolving disease process with continuously declining pancreatic beta-cell function and constant upward creep of hemoglobin A_{1c}, drug therapy needs periodic review and change. Prior to oral drug combination use, about 65% of Type 2 patients started on oral medication, but after 15 years, only 25% remained solely on oral medication.²² Over the same time span the percentage of patients using insulin increased from 20 to 60%. Overall, about 36% of Type 2 patients are insulin-dependent.

Conclusion

Useful new pharmacologic tools to facilitate the management of Type 2 diabetes have become available just as the results of the Kumamoto study and UKPDS have confirmed and extended the conclusions from DCCT. Tight glucose control can reverse the biochemical consequences of prolonged hyperglycemia and enable patients to stay well, avoid hospitalization and lead more productive lives. Caregivers have focused more intensely not only on glycemic control, but also on concurrent control of blood pressure and hyperlipidemia. Patient education is based on the premise that recruitment of each patient as his own pro-active care manager is the most effective way to achieve long-term control. Guidelines are easily available for both caregivers and patients. Type 2 patients have a life expectancy of at least twenty years after diagnosis. They deserve a plan. Successive stopgaps are no longer adequate for treatment of a lifelong condition. As caregivers with patient medication profiles, pharmacists have an excellent opportunity to monitor medication compliance and to provide information and advice on drugs, home glucose measurement, and practical ways for patients to become successful managers. ■

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