الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

السنة الثالثة

تأثير الأدوية 2

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المحاضرة التاسعة

175

Oral glucose-lowering agents

- Useful in the treatment of patients who have type 2 diabetes and cannot be managed by diet alone
- Patients who have developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents
- Patients with long-standing disease may require combination of glucose-lowering drugs/ insulin
- Insulin is added because of the progressive decline in β cells that occurs due to the disease or aging
- Oral glucose-lowering agents should not be given to patients with type 1 diabetes

Oral Antidiabetic Agents

- Insulin secretagogues
  - Sulfonylureas
  - Glinides
- Insulin sensitizers
  - Biguanides
  - Thiazolidinediones
- α-Glucosidase inhibitor
- Dipeptidyl peptidase-IV inhibitors

SGLT2 inhibitors

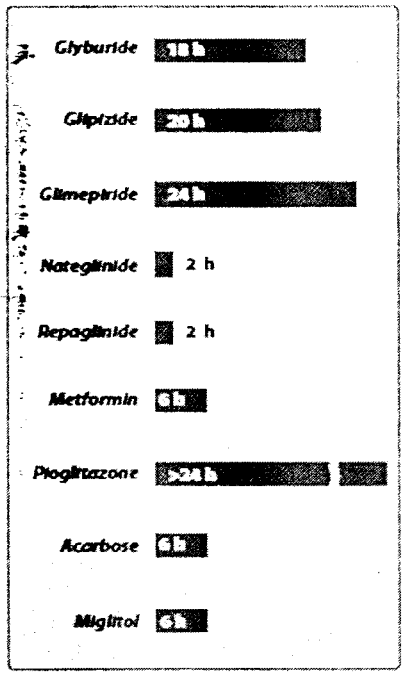


Figure 25.10
Duration of action of some oral hypoglycemic agents.

Oral glucose-lowering agents

- Insulin secretagogues:

Promote insulin release from the β cells of the pancreas

- Sulfonylureas
  - Glibenclamide (Glucocare®, Gluconil®, Declamide®, Daonil®)
  - Glimepiride (Amaryl®)
  - Glipizide(Gluco-Rite®)

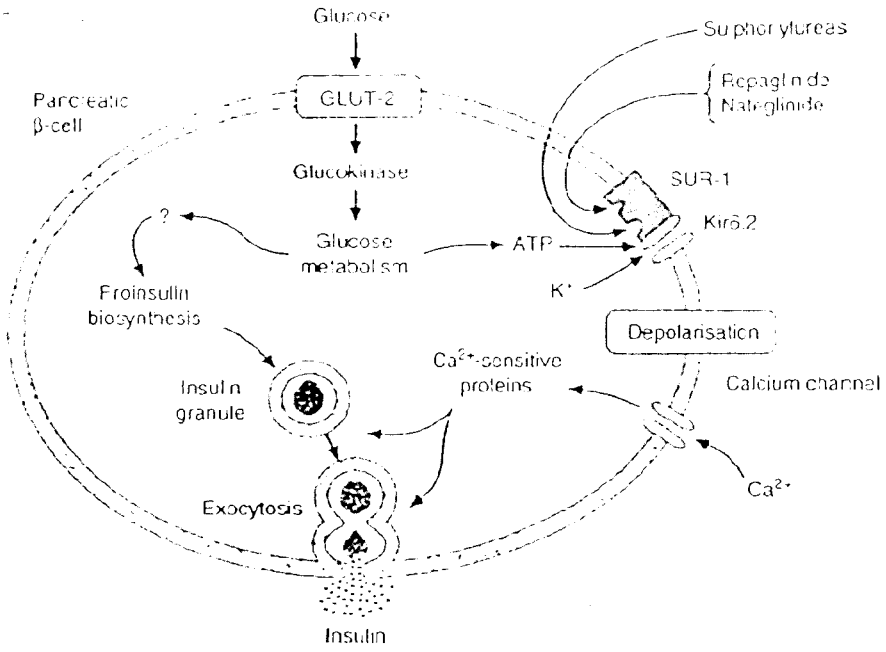
- Glinides
  - Repaglinide (Novonorm®)
  - Nateglinide

Sulfonylureas

- Promote insulin release from the β cells of the pancreas
- The primary drugs used today are the second-generation drugs glibenclamide, glipizide, and glimepiride

- **Mechanism of action:**

1) Stimulation of insulin release from the β cells of the pancreas by blocking the ATP-sensitive K^+ channels, resulting in depolarization and Ca^{2+} influx
2) Reduction in hepatic glucose production
3) Increase in peripheral insulin sensitivity



Antidiabetic Drugs other than Insulin. **Figure 1** Sulphonylureas stimulate insulin release by pancreatic β-cells. They bind to the sulphonylurea receptor (SUR-1), which closes Kir6.2 (ATP-sensitive) potassium channels. This promotes depolarisation, voltage-dependent calcium influx, and activation of calcium-sensitive proteins that control exocytotic release of insulin.

Sulfonylureas

Adverse effects:

- Weight gain
- Hyperinsulinemia
- Hypoglycemia

- Should be used with caution in patients with hepatic or renal insufficiency, because drug accumulation may cause hypoglycemia
- Renal impairment is a particular problem in the case of agents metabolized to active compounds like glibenclamide
- Glibenclamide has minimal transfer across the placenta and may be a safe alternative to insulin therapy in pregnancy

Sulfonylureas drug interactions

- All sulfonylureas are metabolized in theliver
  - CYP2C9 involved in sulfonylurea metabolism

Drug Interactions with Sulfonylureas	
Interaction	**Drugs**
Displacement from protein binding sites[a]	warfarin, salicylates, phenylbutazone, sulfonamides
Alters sulfonylurea hepatic metabolism (cytochrome P450)	chloramphenicol, monoamine oxidase inhibitors, cimetidine, rifampin[b]
Altered renal excretion	allopurinol, probenecid

[a]Many drug interactions metabolism-based

[b]Inducer

Glinides

- Repaglinide
- Nateglinide

Mechanism of action:

- Like the sulfonylureas, their action is dependent on functioning pancreatic β cells
- They bind to ATP-sensitive potassium channels leading to release of insulin
- Categorized as **postprandial glucose regulators**; they are particularly effective in early release of insulin after a meal

Glinides

- The glinides have a rapid onset and a short duration of action, Well absorbed orally after being taken 1 to 30 minutes before meals

- Combined therapy of these agents with metformin or the glitazones is better than monotherapy in improving glycemic control

- Glinides should not be used in combination with sulfonylureas (overlapping MOA)

Glinides

- Metabolized to inactive products by CYP3A4
- Drugs that inhibit CYP3A4 (ketoconazole, itraconazole, fluconazole, erythromycin, and clarithromycin) may enhance the glucose-lowering effect of repaglinide
- Drugs that increase levels of CYP3A4 (barbiturates, carbamazepine, and rifampin) may decrease their glucose lowering effect

- Excreted through the bile
- Repaglinide concurrent use with gemfibrozil is contraindicated due to reports of severe hypoglycemia

Glinides

Adverse effects

- Hypoglycemia (lower incidence than sulfonylureas)
- Weight gain (less than with sulfonylureas)
- Must be used with caution in patients with hepatic impairment

Insulin sensitizers

- Insulin sensitizers improve insulin action
- Lower blood sugar by improving target-cell response to insulin without increasing pancreatic insulin secretion

- Biguanides
- Thiazolidinediones

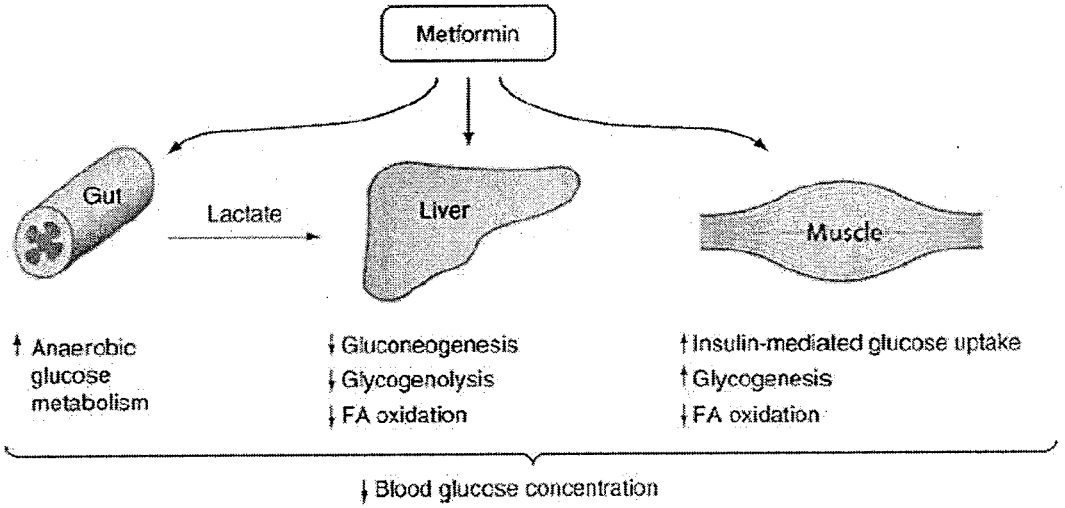
Biguanides

- Metformin (Glucomet®, Glucophage®, Diamet)®
- Increases glucose uptake and use by target tissues, decreasing insulin resistance
- Does not promote insulin secretion (hyperinsulinemia is not a problem)
- The risk of hypoglycemia is less than with sulfonylureas

Metformin

Mechanism of action:

- Reduces hepatic glucose output by inhibiting hepatic gluconeogenesis
- Slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization
- Reduce hyperlipidemia (LDL and VLDL cholesterol concentrations fall, and HDL cholesterol rises)
- The patient commonly loses weight because of loss of appetite



Antidiabetic Drugs other than Insulin. Figure 3 The antihyperglycaemic effect of metformin involves enhanced insulin-mediated suppression of hepatic glucose production and muscle glucose uptake. Metformin also exerts non-insulin-dependent effects on these tissues, including reduced fatty acid oxidation and increased anaerobic glucose metabolism by the intestine. FA, fatty acid; ↑, increase; ↓ decrease.

Metformin

- The ADA recommends metformin as the drug of choice for newly diagnosed type 2 diabetics
- Metformin may be used alone or in combination with one of the other agents as well as with insulin
- Hypoglycemia may occur when metformin is taken in combination with insulin

Metformin

- Metformin is well absorbed orally
- Not bound to serum proteins
- Not metabolized
- Excreted via the urine

Metformin

Adverse effects:

- GI adverse effects
- Metformin is contraindicated in diabetic patients with renal and/or hepatic disease and in those with diabetic ketoacidosis
- Should be discontinued in cases of acute MI, exacerbation of CHF, and severe infection
- Rarely fatal lactic acidosis has occurred
- Long-term use may interfere with vitamin B12 absorption

- Metformin is effective in the treatment of polycystic ovary disease
- Its ability to lower insulin resistance in these women can result in ovulation and possibly pregnancy

Thiazolidinediones (glitazones)

- Insulin sensitizers (Insulin is required for their action)
- Do not promote insulin release (Hyperinsulinemia is not a risk)

- Troglitazone (withdrawn after deaths from Hepatotoxicity)
- Pioglitazone (Actos®)
- Rosiglitazone (Avandia®)

Thiazolidinediones (glitazones)

Mechanism of action

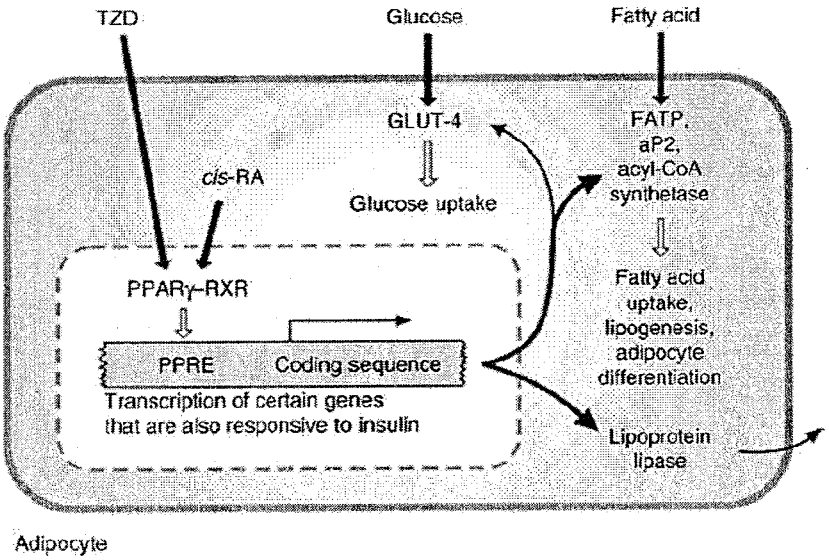
- TZDs target the PPARγ
- Ligands for PPARγ regulate:
  adipocytes differentiation and lipogenesis
  glucose metabolism
  resulting in: increased insulin sensitivity in adipose tissue, liver, and skeletal muscle

- Hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and elevated HbA1c levels are improved
- LDL levels are not affected by pioglitazone
- LDL levels have increased with rosiglitazone
- HDL levels increase with both drugs

Thiazolidinediones (glitazones)

- Pioglitazone and rosiglitazone can be used as monotherapy or in combination with other glucose- lowering agents or insulin
- The dose of insulin required for adequate glucose control in these circumstances may have to be lowered
- Pioglitazone is recommended as a tier 2 alternative for patients who fail or have contraindications to metformin therapy
- **Pioglitazone** is associated with a slightly higher risk of **bladder cancer**

Rosiglitazone is not recommended due to concerns regarding **cardiac adverse effects**



Antidiabetic Drugs other than Insulin. Figure 4 Thiazolidinediones stimulate the PPARγ moiety of the PPARγRXR nuclear receptor complex, which then binds to a response element, leading to transcription of certain genes that are also responsive to insulin. These facilitate increased uptake of fatty acids, lipogenesis and adipogenesis. PPARγ, peroxisome proliferator-activated receptor-γ; RXR, retinoid X receptor; PPRE, peroxisome proliferator response element; TZD, thiazolidinedione; *cis*-RA, *cis*-retinoic acid; GLUT-4, glucose transporter isoform-4; FATP, fatty acid transporter protein; aP2, adipocyte fatty acid binding protein.

Thiazolidinediones

- Extensively bound to serum albumin
- Both undergo extensive metabolism by CYP450
- Some metabolites of pioglitazone have activity
- Elimination of pioglitazone and its metabolites is mainly in the bile
- The metabolites of rosiglitazone are primarily excreted in the urine

Thiazolidinediones

Adverse effects

- Very few cases of liver toxicity with rosiglitazone or pioglitazone. Because of deaths due to hepatotoxicity from troglitazone it is recommended that liver enzyme are periodically checked
- Weight increase can occur
- Osteopenia and increased fracture risk
- Increased risk of myocardial infarction and death from cardiovascular causes with rosiglitazone
- Headache
- Anemia
- May cause resumption of ovulation in some women who have been anovulatory
- Premenopausal women should be counseled about the need for adequate contraception while taking TZDs

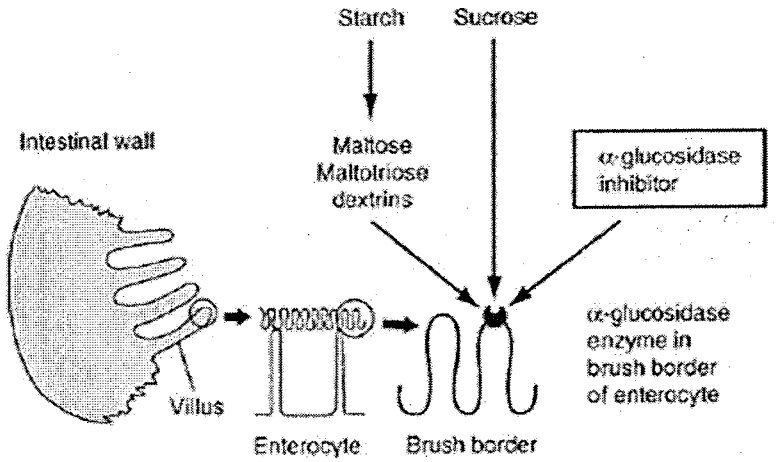
α-Glucosidase inhibitors

- Acarbose (Acrose®, Prandase®)
- Miglitol

Oral drugs for the treatment of patients with type 2

Mechanism of action

- Taken at the beginning of meals
- Act by delaying the digestion of carbohydrates lowering postprandial glucose levels
- Reversible inhibitors of membrane-bound α-glucosidase in the intestine
- This enzyme is responsible for hydrolysis of oligosaccharides to glucose and other sugars
- Acarbose also inhibits α-amylase, interfering with the breakdown of starch to oligosaccharides
- The postprandial rise of blood glucose is blunted



Antidiabetic Drugs other than Insulin. Figure 5 α-Glucosidase inhibitors slow the rate of intestinal carbohydrate digestion by competitive inhibition of α-glucosidase enzymes in the brush border of enterocytes. The α-glucosidase inhibitors have a higher affinity for the α-glucosidase enzymes than the natural disaccharide and oligosaccharide substrates.

α-Glucosidase inhibitors

Adverse effects

- Flatulence, diarrhea, and abdominal cramping
- Patients with IBD, colonic ulceration, or intestinal obstruction should not use these drugs
- No hypoglycemia if used alone
- Hypoglycemic patient should be treated with glucose rather than sucrose, because sucrose is also inhibited by these drugs

Dipeptidyl peptidase-IV (DPP-4) inhibitors

- Sitagliptin (Januvia®)
- Saxagliptin (Onglyza®)
- Vildagliptin (Galvus®)
- Linagliptin (Tradjenta®)
- Orally active DPP-4 inhibitors used for the treatment of patients with type 2 diabetes
- Combinations with metformin are available
  - Sitagliptin + metformin (Januet®)
  - Vildagliptin + metformin (Eucreas®)

DPP-4 inhibitors

Mechanism of action

- Inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones such as GLP-1

- Prolonging the activity of incretin hormones results in increased insulin release in response to meals and reduction in glucagon secretion

DPP-4 inhibitors

- DPP-4 inhibitors may be used as monotherapy or in combination with a sulfonylurea, metformin, glitazones, or insulin
- Sitagliptin and saxagliptin are excreted in urine
  - Dosage adjustments for both DPP-4 inhibitors are recommended for patients with renal dysfunction
- Saxagliptin is metabolized by CYP450
  - Strong inhibitors of CYP3A4/5, such as nelfinavir, atazanavir, ketoconazole, and clarithromycin, may increase levels of saxagliptin

Adverse effects

- Nasopharyngitis
- Headache
- Pancreatitis has occurred with sitagliptin

Sodium-glucose cotransporter 2 inhibitors

- Dapagliflozin (Forxiga)®
- Canagliflozin

Mechanism of action:

- SGLT2 is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney
- By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose
- Decreases reabsorption of sodium and causes osmotic diuresis reducing systolic blood pressure

SGLT inhibitors

- Given once daily in the morning
- Canagliflozin should be taken before the first meal of the day
- Metabolized by glucuronidation to inactive metabolites
- Should be avoided in patients with renal dysfunction

Adverse effects:

- Female genital mycotic infections and urinary tract Infections frequency
- Hypotension

Other agents

- Bromocriptine and colesevelam produce modest reductions in HbA1c
- The mechanism of action of glucose lowering is unknown
- Indicated for type 2 diabetes
- Modest efficacy, adverse effects limit their use in clinical practice

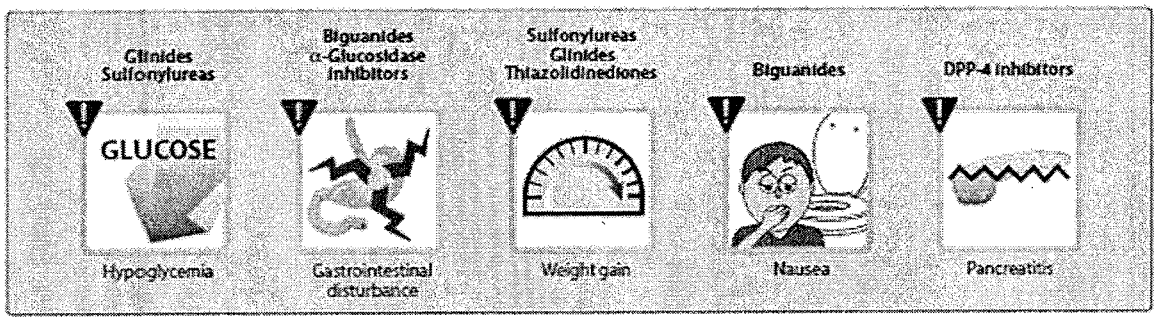


Figure 25.11
Some adverse effects observed with oral hypoglycemic agents.

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate / Severe; Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra-indicated CKD Stage 3B-4-5	Exenatide Contra-indicated eGFR <30	Genital Mycotic Infections	Dose Adjustment May be Necessary (Except Linagliptin)	Neutral	May Worsen Fluid Retention	More Hypo Risk	Neutral	Neutral	More Hypo Risk & Fluid Retention	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit		Increased LDL			Neutral	?		Safe		
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects

Monotherapy, Dual Therapy, and Triple Therapy for T2D

Monotherapy	Dual therapy	Triple therapy
Metformin	GLP1RA	GLP1RA
GLP1RA	SGLT2I	SGLT2I
SGLT2I	DPP4I	TZD†
DPP4I	TZD†	Basal insulin†
AGI	Basal insulin†	DPP4I
TZD†	Colesevelam	Colesevelam
SU/glinide†	BCR-QR	BCR-QR
	AGI	AGI
	SU/glinide†	SU/glinide†

AGI = α-glucosidase inhibitors; BCR-QR = bromocriptine quick release; Coles = colesevelam; DPP4I = dipeptidyl peptidase 4 inhibitors; GLP1RA = glucagon-like peptide 1 receptor agonists; Met = metformin; SGLT2I = sodium-glucose cotransporter 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinediones.

*Intensify therapy whenever A1C exceeds individualized target. Boldface denotes little or no risk of hypoglycemia or weight gain, few adverse events, and/or the possibility of benefits beyond glucose-lowering.

† Use with caution.

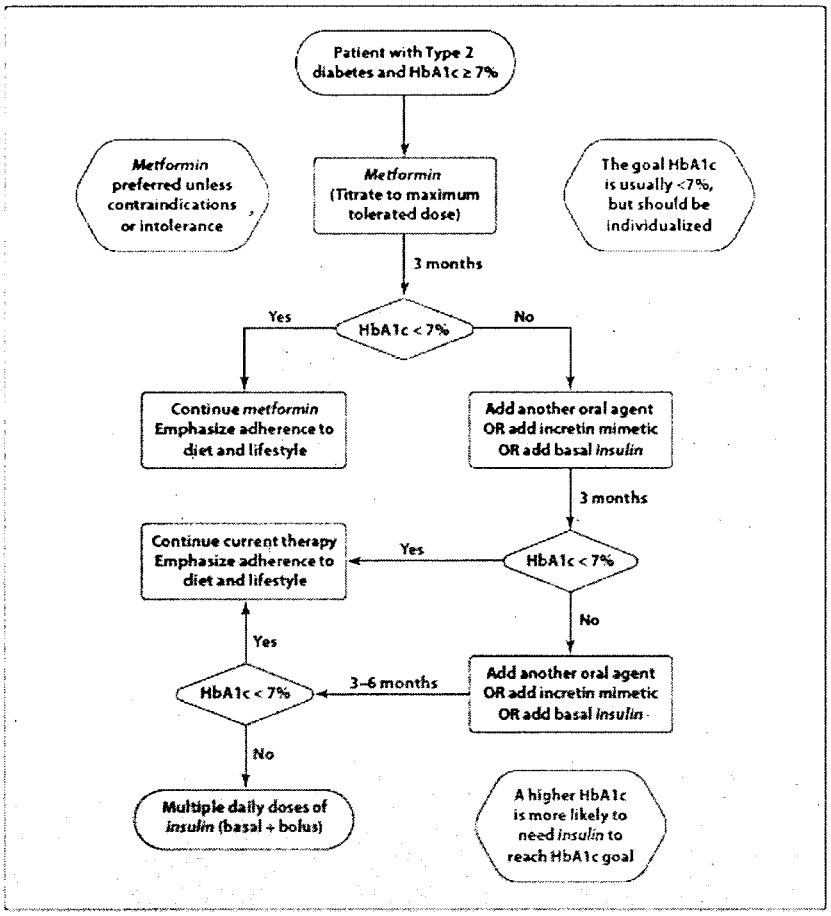


Figure 25.14
Treatment guidelines for type 2 diabetes.

agent[79]	mechanism[1]	advantages[79]	disadvantages[79]
Sulfonylurea (glyburide, glimepiride, glipizide)	Stimulating insulin release by pancreatic beta cells by inhibiting the K_{ATP} channel	• Inexpensive • Fast onset of action • No effect on blood pressure • No effect on low-density lipoprotein • lower risk of gastrointestinal problems than with metformin • more convenient dosing	• Causes an average of 5–10 pounds weight gain • Increased risk of hypoglycemia • Glyburide has increases risk of hypoglycemia slightly more as compared with glimepiride and glipizide
Metformin	Acts on the liver to reduce gluconeogenesis and causes a decrease in insulin resistance via increasing AMPK signalling.	• Not associated with weight gain • Low risk of hypoglycemia as compared to alternatives • Good effect on LDL cholesterol • Decreases triglycerides • No effect on blood pressure • Inexpensive	• Increased risk of gastrointestinal problems • Due to risk of potentially fatal lactic acidosis, contraindicated for people in shock, with acute or chronic, moderate or severe kidney disease or at risk for impaired kidney function from intravenous dye, and with acute or chronic metabolic acidosis • Risk of lactic acidosis also is increased for people with unstable or acute heart failure, liver disease, or alcoholism, or who are recovering from major surgery • Increased risk of Vitamin B12 deficiency[1] • Less convenient dosing • Metallic taste[1]
Alpha-glucosidase inhibitor (acarbose, miglitol, voglibose)	Reduces glucose absorbance by acting on small intestine to cause decrease in production of enzymes needed to digest carbohydrates	• Slightly decreased risk of hypoglycemia as compared to sulfonylurea • Not associated with weight gain • Decreases triglycerides • No effect on cholesterol	• Less effective than most other diabetes pills in decreasing glycated hemoglobin • Increased risk of GI problems than other diabetes pills except metformin • Inconvenient dosing • Expensive
Thiazolidinediones (Pioglitazone, Rosiglitazone)	Reduce insulin resistance by activating PPAR-γ in fat and muscle	• Lower risk of hypoglycemia • Slight increase in high-density lipoprotein • Actos linked to decreased triglycerides • Convenient dosing	• Increased risk of heart failure • Causes an average of 5–10 pounds weight gain • Associated with higher risk of edema • Associated with higher risk of anemia • Increases low-density lipoprotein • Avandia linked to increased triglycerides and risk of heart attack • Actos linked to increased risk of bladder cancer • Slower onset of action • Requires monitoring for hepatotoxicity • Associated with increased risk of limb fractures • Expensive