



## Antidiabetic Agents

Updated: June 6, 2017.

### OVERVIEW

Management and treatment of diabetes usually begins with advice on diet and exercise. Insulin is the therapeutic mainstay of therapy of type 1 diabetes, whereas agents that increase insulin secretion or activity are the primary approaches to therapy of type 2 diabetes. First line conventional therapies for type 2 diabetes include biguanides (metformin) and sulfonylureas. Metformin increases insulin sensitivity whereas the sulfonylureas increase insulin secretion. More recently developed agents include alpha glucosidase inhibitors, thiazolidinediones, metiglidine analogues and drugs that affect the incretin system. Alpha glucosidase inhibitors act in the gastrointestinal tract to decrease glucose absorption. The thiazolidinediones affect multiple intracellular metabolic pathways that increase insulin actions and improve insulin sensitivity. Metiglidines, like the sulfonylureas, increase insulin secretion. Finally, drugs that affect the incretin system include analogues of glucagon-like peptide-1 (GLP-1) that promote early insulin release from the pancreas and inhibitors of dipeptidyl peptidases 4 (DPP-4) that prolong the activity of GLP-1 in the serum. A relatively new category of antidiabetic agents are inhibitors of the sodium glucose cotransporter-2 (SGLT-2), which is responsible for reabsorption of glucose in the kidney; inhibition of this transporter causes glucosuria and can reduce hyperglycemia in patients with diabetes. The first commercially available SGLT-2 inhibitors (canagliflozin and dapagliflozin) were approved for use in the United States in 2013. Most antidiabetic agents have minimal adverse effects on the liver and have only rarely been linked to instances of clinically apparent acute liver injury.

- Alpha-Glucosidase Inhibitors
  - Acarbose
  - Miglitol
- Incretin-Based Drugs
  - Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
    - Alogliptin
    - Linagliptin
    - Saxagliptin
    - Sitagliptin
  - Glucagon-Like Peptide-1 (GLP-1) Analogues
    - Albiglutide
    - Dulaglutide
    - Exenatide
    - Liraglutide
    - Lixisenatide
    - Semaglutide
- Insulin

- Metformin
- Metiglinide Analogues
  - Nateglinide
  - Repaglinide
- Pramlintide
- Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitors
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin
  - Ertugliflozin
- Sulfonylureas
  - First Generation Sulfonylureas
    - Acetohexamide
    - Chlorpropamide
    - Tolazamide
    - Tolbutamide
  - Second Generation Sulfonylureas
    - Gliclazide
    - Glimepiride
    - Glipizide
    - Glyburide (Glibenclamide)
- Thiazolidinediones
  - Pioglitazone
  - Rosiglitazone
  - Troglitazone

## ANNOTATED BIBLIOGRAPHY

References updated: 06 June 2017

Zimmerman HJ. Oral hypoglycemic agents and other diabetes therapy. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999; pp. 575-9.

*(Textbook of hepatotoxicity published in 1999, discusses hepatotoxicity of sulfonylureas, thiazolidinediones, acarbose and metformin).*

De Marzio DH, Navarro VJ. Alpha-glucosidase inhibitors. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 529-30. (Recent review of hepatotoxicity of drugs for diabetes

).

Powers AC, D'Alessio D. Therapy of diabetes. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1248-67.

*(Textbook of pharmacology and therapeutics).*

Davis SN. Insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006, pp. 1613-88.

*(Textbook of pharmacology and therapeutics).*

Drugs for type 2 diabetes. *Treat Guidel Med Lett* 2014; 12 (139): 17-24. PubMed PMID: 24566424.

*(Concise review of current therapy of type 2 diabetes).*

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN Prospective Study. *Gastroenterology* 2015; 148: 1340-52. PubMed PMID: 25754159.

*(Among 899 cases of drug induced liver injury in the US collected between 2004 and 2012, 4 cases were attributed to drugs used for diabetes [metformin, glyburide, sitagliptin], but no cases were attributed to acarbose or a thiazolidinedione).*

Drugs for type 2 diabetes. *Med Lett Drugs Ther* 2017; 59 (1512): 9-18. PubMed PMID: 28076339.

*(Concise summary of the mechanisms of action, efficacy, safety and costs of currently available drugs for type 2 diabetes; mentions that serum enzyme elevations can occur with acarbose therapy and that hepatitis and liver failure have been described with thiazolidinedione and DDP-4 inhibitor therapy).*