For the treatment of Type-2 diabetes mellitus, currently the ADA recommends beginning with **metformin** along with life-style changes (exercise, diet). If this therapy fails to maintain normal glucose levels, then protocol should be followed with insulin and/or oral antidiabetic drugs, according to medical criteria.

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A.2 Type-II Antidiabetic Agents

- Before the 1980s, sulfonylureas were the only oral antidiabetic agents for the treatment of Type-II diabetes. **Tolbutamide (Orinase^{R})**, developed in Germany by Hoechst (1950s), was the first oral antidiabetic agent.

However, since then an explosion of new classes of Type-II-antidiabetic agents has developed. The following approaches are considered:

- *Agents that increase the secretion of insulin by the pancreas.*
- *Agents that increase the sensitivity of target organs to insulin (sensitizers).*
- *Agents that decrease the glucose absorption from the GI tract.*
- *Agents that inhibit glucose reabsorption in the kidney.*

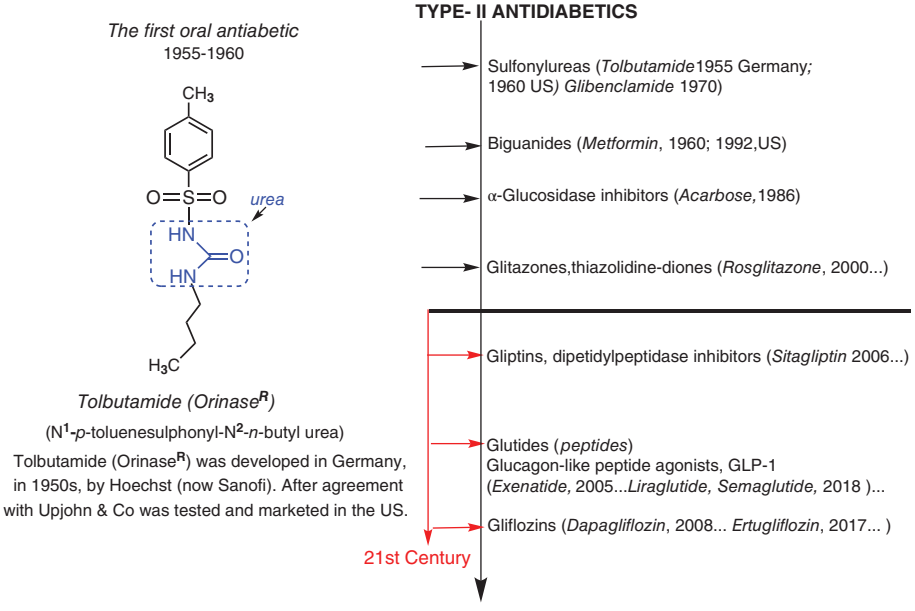

Figure 1.A.1 *Type-II antidiabetic agents*. Historic evolution of the oral antidiabetic discovery. The first oral antidiabetic to be used was the sulphonyl urea **Tolbutamide,** (**Orinase**). Developed in Germany,it was soon marketed in the US. According to t***he Upjohn Memories website***: *Through a research agreement with Hoechst of Germany we made and tested Orinase clinically in the US. When it proved to be an effective oral anti-diabetic we developed an improved process and began a full-scale manufacturing process in 1957.*


(a) (b)

Figure 1.A.2 (a) *Galega officinalis* L. (*Fabaceae*). Northern Spain. (b) *Galega officinalis* L. (*Fabaceae*). Pictures provided by botanists José Ramón López Retamero and Pello Urrutia (*Herbario Digital Xavier de Arizaga, HXDA)*.

Figures 1.A.1–1.A.4 represent the different classes of Type-II antidiabetic agents:

- *BIGUANIDES (1990) Plant-derived antidiabetic agents.*
- *GLIPTINS (2005) Non plant-derived antidiabetic agents.*
- *GLUTIDES (2005) Non plant-derived antidiabetic agents.*
- *GLIFLOZINS (2010) Plant-derived antidiabetic agents.*

- **Guanidines hypo-glycemiants. Biguanides.**

Diabetes has been treated historically with plant extracts. One medicinal plant, *Galega officinalis* L. (*Fabaceae*) *Goat's rue*, led to the discovery of **metformin.**

The use of biguanides can be traced back to the Middle Ages.The plant *Galega officinalis* L. was used as galactogen in animals (cows) but also in infusion to alleviate the intense urination associated with diabetes, a disease unknown at that time. Galegin (isoamylene-guanidine) was isolated in 1914, by Tanret, from seeds of *Galega*.

- *Derived from **galegine,** one prototype molecule found in a plant with a long history of medicinal use,* **metformin** *exemplifies an efficacious drug discovery based on the use of a plant to treat the diabetes.*

The first hypoglycemic agents tested and studied before the isolation of insulin were guanidine derivatives of natural origin. *Galega officinalis* contains the biguanide **galegine** (isoamylene guanidine) that has been shown to have blood-glucose lowering effects.

At the beginning of the twentieth century galegine was used as a crystalline sulphate. It was extracted from the seeds of *Galega officinalis* with alcohol 60° (Tanret, 1914).

The natural guanidines, galegine (and **agmatine,** from herring sperm) were used as hypoglycemic drugs. Although galegine produces positive results, its activity was weak and variable; its use was discontinued.

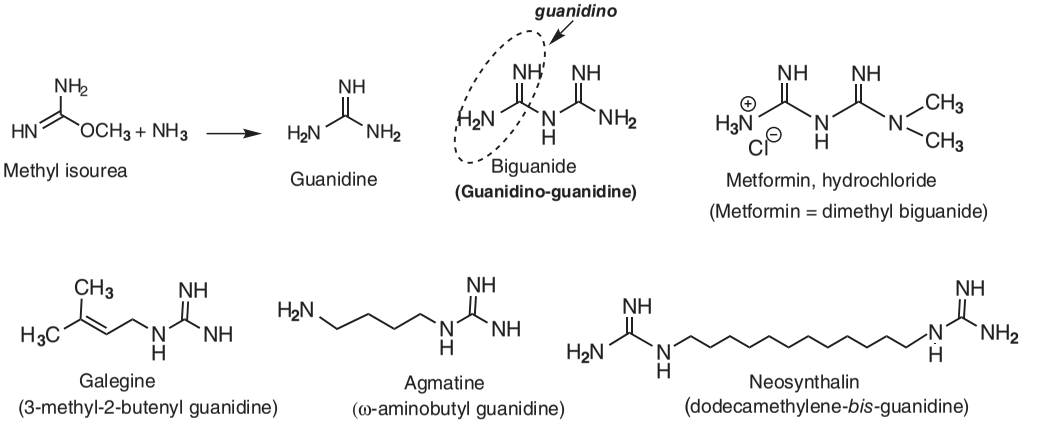

Figure 1.A.3 Guanidines hypo-glycemiants. Metformin is the front line (plus diet and exercise) in the treatment of Type-II diabetes.

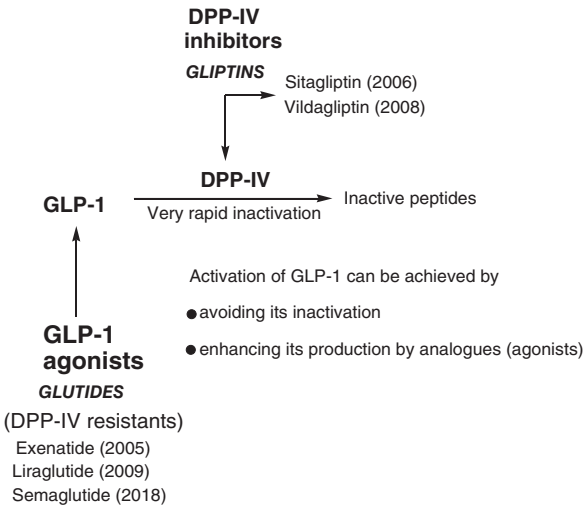

Figure 1.A.4 Glucagon-like peptide (GLP-1). *Source:* Appendix Reference [1].

Professor Carl Slotta, at the Chemistry Institute of the University of Vienna synthesized a series of compounds with guanidine groups at each end of a long polymethylene chain.

From 1927, the synthetic guanidines **synthalin A** (decamethylene-*bis*-guanidine) and **neosynthaline** (dodecamethylene-*bis*-guanidine) began to be used but were also discontinued because of hepatic toxicity associated with their use. At that time it was known that the administration of guanidine hydrochloride to experimental animals caused convulsions associated with hypoglycemia; this was reversible, with difficulty, by intravenous administration of glucose.

In 1957–1958, the biguanides **metformin** (dimethylbiguanide), **phenformin** (phenethylbiguanide) and **buformin** (*n*-butyl biguanide) were introduced. Biguanides do not produce hypoglycemia, but reduce basal and postprandial hyperglycemia in diabetes. They were also withdrawn from use as they induce lactic acidosis.

In 1990, metformin was reintroduced in many countries, such as the US, where it was approved in 1994.

- *Derived from* ***galegine,*** *one prototype molecule found in a plant with a long history of medicinal use,* **metformin** *exemplifies an efficacious drug discovery based on the use of a plant to treat the diabetes.*

A.3 Biguanides

This class of agents is capable of reducing sugar absorption from the GI tract. They decrease gluconeogenesis and increase glucose uptake by muscles and cells. These effects lead to lower glucose levels.

Unlike sulfonylureas, biguanides are not hypoglycemic agents but rather act as antihyperglycemic drugs.

- *Biguanides do not stimulate insulin secretion and, therefore, do not cause hypoglycemia.*
- *Biguanides do not induce weight gain, which is very useful for insulin-resistant obese patients.*

Currently, metformin is the front-line for type-2 diabetic patients.

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- **Gliflozins are described in Chapter 2.**

***

Non plant derived antidiabetic agents developed in the 2000s (Summary).

- **GLUCAGON-LIKE PEPTIDE-1, GLP-1 a valuable target for developing Type-II antidiabetic agents: *Gliptins and Glutides*[1]**

GLP-1 (GLUCAGON-LIKE PEPTIDE) is a 36 aminoacid peptide intestinal incretin hormone secreted in the gut and released in the bloodstream in response to food intake.

GLP-1 has a clearly established role in glucose-dependent insulin secretion. It works by increasing insulin release from the pancreas and decreases excessive glucagon release.

GLP-1 also inhibits glucagon release after meals and slows gastric emptying, promoting a feeling of satiety and decreasing appetite (Figure 1.A.4).

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GLP-1-analogue **exenatide** (2005, **Byetta**^{R}) is the synthetic version (Merrifield coupling methodology) of exendin-4, a peptide (39 *aa*) discovered in the saliva of the Gila monster lizard *Heloderma suspectum* that lives in desert regions of Arizona and North Mexico, USA (*Who would have ever thought that Gila monster lizard saliva would be a good place to start looking for a type-II antidiabetics*).

Further acylated peptides GLP-1 (7–37) derivatives, with acyl moieties ranging from 12–18 carbons were developed. **Liraglutide** and **semaglutide (Ozempic^{R})** arose from this research.

Semaglutide is an antidiabetic indicated for the treatment of type 2 diabetes and an anti-obesity medication used for long-term weight management. It is a glucagon-like peptide-1 receptor agonist, peptide similar to the hormone glucagon-like peptide-1 (GLP-1), variously modified, amongst others, with a fatty acid side chain.

Reference

1 Knudsen, J.B. (2004). Glucagon like-peptide-1: the basis of a new class of treatment of type-II diabetes. *J. Med.* Chem (47): 4128–4134.

1 For the origin and a brief description of Dipeptidyl-Peptidase-IV Inhibitors (*Gliptins*) and peptides that mimic the blood-sugar-lowering activity of Glucagon-Like-Peptide 1 (GLP-1) (*Glutides*), see '*The Evolution of Drug Discovery. From traditional medicines to modern drugs*'. Wiley-VCH, 2011, pages 434–439.