Metformin

From Research to Clinical Practice

Meng H. Tan, MD[a,*], Hussain Alquraini, MD[a], Kara Mizokami-Stout, MD[a], Mark MacEachern, MLIS[b]

KEYWORDS

- Metformin • Glucose-lowering drug • Type 2 diabetes mellitus
- Polycystic ovary syndrome • Delaying onset of type 2 diabetes mellitus
- Gestational diabetes

KEY POINTS

- Metformin is the first-line glucose-lowering drug to control hyperglycemia in type 2 diabetes mellitus (T2DM); an insulin sensitizer, it decreases hepatic gluconeogenesis and increases glucose disposal in skeletal muscles.
- Metformin is safe (small risk for hypoglycemia, weight neutral, and some gastrointestinal [GI] adverse events), is inexpensive, reduces microvascular complication risk, and lowers cardiovascular mortality compared with sulfonylurea therapy.
- Metformin-induced lactic acidosis is rare; metformin-associated lactic acidosis (MALA) is often caused by other conditions.
- Guidelines for metformin's use in T2DM patients with mild to moderate renal impairment and congestive heart failure have changed.
- Metformin is also used to delay the onset of T2DM, in treating gestational diabetes mellitus (GDM) (especially outside the United States), and in women with polycystic ovary syndrome (PCOS).

INTRODUCTION

Many professional diabetes organizations recommend metformin (provided there are no contraindications for its use) as the first glucose-lowering drug (GLD) to be initiated when lifestyle therapies for T2DM do not achieve glycemic target.[1–4] Metformin has emerged as the preferred first GLD as new knowledge on T2DM and metformin is

The authors have nothing to disclose.

[a] Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA; [b] Taubman Health Sciences Library, University of Michigan, Ann Arbor, MI, USA

* Corresponding author. Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, 24 Frank Lloyd Wright Drive, Lobby G, Suite 1500, Ann Arbor, MI 48106.

E-mail address: mengt@med.umich.edu

Endocrinol Metab Clin N Am 45 (2016) 819–843
http://dx.doi.org/10.1016/j.ecl.2016.06.008 **endo.theclinics.com**

uncovered by research and translated into clinical practice. This article's aim is to review selected aspects of this new knowledge (identified in a literature search of PubMed, Embase, and Cochrane Central Register of Controlled Trials in November 2015) reported since 2000. Specifically, the focus is on

1. Use in T2DM
2. Use in other diseases and conditions
3. Current research that may lead to more pleiotropic effects

This review discusses some old concepts of this 59-year-old (as of 2016) GLD that have changed, yielding to new ones.

USE IN TYPE 2 DIABETES MELLITUS

Drug Development

Metformin (dimethylguanidine) has its roots in a plant, *Galega officinalis* (French lilac, Goat's rue, or Spanish sainfoin), rich in guanidine. An outline of the events from 1918, when guanidine was shown to lower blood glucose in animals, to its launch as an oral GLD in 1957 and beyond is shown in **Table 1**.[5]

The First-Line Oral Glucose-Lowering Drug for Type 2 Diabetes Mellitus

The only approved indication for metformin use is as "an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus."[6] The package insert reports the clinical trials results that led to this indication. Meta-analysis and systematic reviews of metformin monotherapy (**Table 2**) support its glucose-lowering effect in T2DM patients.[7–10]

Table 1
Development of metformin from plant to glucose-lowering drug

Year	Drug Development Events
Late 1800s	*Galega officinalis* — rich in guanidine
1918	Guanidine lowers blood glucose in animals
1920s	Guanidine is toxic; isoamylene guanidine less toxic
1920s–early 1930s	Synthalin A (decamethylene diguanide) and synthalin B (dodecamethylene diguanide) synthesized
1929	Flumamine (dimethylbiguanide) synthesized and used for treating influenza in the Philippines. This intrigued clinical pharmacologist Jean Sterne in France to investigate the glucose-lowering effect of this drug.
1957	Sterne published article on the glucose-lowering properties of dimethylbiguanide and proposed the name Glucophage (glucose eater) for metformin.
1958	Metformin launched in United Kingdom
1957 and 1958	Clinical trials with more potent biguanides phenformin and buformin reported.
1970s	Both phenformin and buformin withdrawn because of their association with lactic acidosis.
1972	Metformin launched in Canada
1995	Metformin launched in the US
2004	Metformin ER available
2016	DR metformin acts in ileum and lowers blood glucose.