

# **Literature Review of Drug (Metformin)**

## **Introduction**

Metformin is a cornerstone drug in the treatment of type 2 diabetes mellitus (T2DM), recognized for its ability to improve glycemic control primarily by reducing hepatic glucose production. This review details the discovery process of metformin, its clinical trial phases, therapeutic applications, and market impact, supported by key references from PubMed, NCBI, and Google Scholar.

## **Drug Discovery Process**

The journey of metformin began with the study of plants such as *Galega officinalis* (French lilac), historically used for diabetes symptoms since the 18th century. The active compound, guanidine derivatives, inspired the synthesis of biguanides. Metformin (dimethylbiguanide) was first synthesized by Werner and Bell in 1922 (Bailey, 2017; PubMed ID: 28776081).

Jean Sterne, a French physician working at Aron Laboratories, played a pivotal role in translating metformin's antidiabetic potential into clinical use. In 1957, he published the first clinical report on metformin's glucose-lowering effects with minimal side effects, marking a major milestone (Sterne, 1957; Aston Research Explorer, 2017). Subsequent research in the 1970s and 1980s elucidated metformin's mechanisms including inhibition of gluconeogenesis and increased insulin sensitivity (Bailey, 2017).

Metformin was introduced into clinical practice in Europe in the late 1950s but faced slow adoption in the United States due to concerns about lactic acidosis with related biguanides. It was FDA-approved in the US in 1994 following extensive research and safety evaluation (Bailey, 2017; PubMed ID: 28776081)

## **Clinical Trial Phases**

### **Phase I:**

Early phase trials focused on safety, tolerability, and pharmacokinetics in healthy volunteers and diabetic patients. These studies identified metformin's favorable profile with low risk of hypoglycemia (Bailey et al., 1996).

### **Phase II:**

These dose-ranging studies confirmed metformin's glucose-lowering efficacy and established optimal dosing regimens. The research demonstrated improved fasting plasma glucose and HbA1c levels (Garber et al., 1997).

### **Phase III:**

Landmark large-scale trials, such as the UK Prospective Diabetes Study (UKPDS, 1998), demonstrated the cardiovascular benefits and long-term safety of metformin in overweight type 2 diabetics, reinforcing its role as first-line therapy (UKPDS Group, 1998; PubMed ID: 9708327). Other outcome studies showed metformin's superiority in reducing microvascular complications compared with sulfonylureas (UKPDS)

### **Therapeutic Applications**

Primarily indicated for type 2 diabetes mellitus, metformin improves glycemic control by decreasing hepatic gluconeogenesis and improving peripheral glucose uptake. It is also used off-label for conditions such as polycystic ovary syndrome (PCOS), metabolic syndrome, and for weight management in insulin-resistant patients (Diamanti-Kandarakis & Dunaif, 2012; PubMed ID: 23468360).

Recent mechanistic studies clarify metformin's activation of AMP-activated protein kinase (AMPK), contributing to metabolic regulation and potential anti-aging effects (Foretz et al., 2014). Additionally, metformin shows promising anticancer benefits through modulation of cellular metabolism and immunomodulatory effects (Pernicova & Korbonits, 2014)

### **Market Impact**

Metformin remains one of the most prescribed antidiabetic drugs worldwide. Its introduction transformed diabetes management by offering an effective, safe, and inexpensive oral therapy. Global sales surged following US approval in the 1990s, with metformin becoming available in numerous generic formulations, assuring broad access (Bailey, 2017).

The widespread adoption of metformin is driven by its well-demonstrated efficacy, favorable tolerability, and cardiovascular outcome benefits, supported by robust clinical evidence and global guideline endorsements (ADA Standards of Care, 2024). The drug's market dominance is reinforced by ongoing research exploring novel indications and combination therapies.

### **Conclusion**

Metformin's discovery and clinical development highlight the successful transition from traditional medicine to modern pharmacotherapy. Its enduring clinical relevance arises from extensive validation through clinical trials and a remarkable safety-efficacy balance. Metformin continues to evolve in therapeutic application, maintaining a vital role in diabetes and related metabolic disorder management.

## References

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