

# Beyond diabetes: The beneficial uses of metformin in psychiatry

**Metabolic dysregulation is quite common among psychiatric patients, especially those with psychotic or mood disorders. Obesity, diabetes, and dyslipidemia can be present at the onset of the illness, or as an iatrogenic complication. This often leads to premature mortality due to elevated cardiovascular and cerebrovascular risks.**

Enter metformin. It is the most widely used hypoglycemic agent for type 2 diabetes (T2D), and it is frequently used by psychiatric clinicians. Discovered in 1922 and developed in France in the 1950s, metformin was approved for use in the United States in 1995, 3 decades after its launch in Europe. Its original trade name in the United States was Glucophage, and it is currently available from several companies in generic form. It is included on the World Health Organization list of essential medications.

T2D is currently an epidemic across the general populations globally, especially in the United States, where approximately 95% of the 37 million individuals with diabetes have been diagnosed with T2D.<sup>1</sup> This is 300% higher than the prevalence in the 1970s. No wonder metformin is one

of the most often-used drugs in all of medicine, and a staple in primary care and psychiatry. It has helped countless patients avoid the multisystem hazards of insulin resistance, which is the root cause of T2D.

Metformin exerts its hypoglycemic effects by:

- decreasing glucose production from the liver
- increasing insulin receptors' sensitivity in various body tissues
- increasing secretion of growth differentiating factor, which reduces appetite and calorie intake.

In 2017, the American College of Physicians updated its guidelines to adopt metformin as the first-line treatment for T2D, especially because the class of sulfonylureas were associated with a more than 5-fold higher risk of severe low blood sugar events compared with metformin.<sup>2</sup> In addition, metformin causes weight loss, while sulfonylureas are associated with weight gain. Metformin is particularly useful in gestational diabetes, where babies are born with less visceral fat and are less prone to insulin resistance later in life as adults.

The adverse effects of metformin are dose-related and mostly gastrointestinal (GI), including nausea, vomiting, cramps, diarrhea, and flatulence. Gradual titration or



**Henry A. Nasrallah, MD**  
Editor-in-Chief

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**In addition to its metabolic benefits, this agent has many salutary physical and mental effects**

To comment on this editorial or other topics of interest:  
henry.nasrallah  
@currentpsychiatry.com



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**Table**

**Metformin's mechanisms  
in attenuating the hallmarks  
of aging**

Improving nutrient sensing
Enhancing autophagy
Enhancing intracellular communications
Protecting against macromolecular damage
Delaying stem cell aging
Modulating mitochondrial function
Regulating gene transcription
Lowering telomere attrition
Reducing senescence
Source: Reference 17

using the extended-release formulation can lower or avert GI discomfort. Metformin should not be used in patients with severe kidney or liver disease. With long-term use, metformin can cause malabsorption and eventual deficiency of vitamin B12.

The metabolic benefits of metformin listed below are why psychiatrists use it in clinical practice. However, this medication has several benefits that go beyond metabolic disorders. Clinicians should be aware of all of the following salutary physical and mental effects of metformin.

**Metabolic benefits**

- Decreasing glucose dysregulation with the use of clozapine and other antipsychotics.<sup>3</sup>
- Decreasing weight, body mass index, and waist circumference with the use of clozapine.<sup>4</sup>
- Decreasing triglycerides and total cholesterol.<sup>5</sup>
- Mitigating clozapine-induced obesity, especially if used prophylactically.<sup>6</sup>
- Lowering antipsychotic-induced weight gain.<sup>7</sup>

**Nonmetabolic benefits**

- Lowering elevated serum prolactin levels to avert sexual dysfunction.<sup>8-10</sup>
  - Increasing the production of neurons by inducing neurogenesis.<sup>11,12</sup>
  - Activating the cerebral cortex to blunt the adverse effects of clozapine (such as deterioration of motivation, attention, cognition, and behavior) and increasing the activity of the dopamine D1 receptor, which is believed to be involved with cognition in schizophrenia.<sup>13</sup>
  - Reducing the symptoms of anxiety and depression by increasing serotonin activity and hippocampal concentration of serotonin.<sup>14</sup>
  - Decreasing the depressive symptoms known to be associated with uncontrolled diabetes.<sup>15</sup>
  - Improving insulin resistance associated with polycystic ovary syndrome and helping with infertility.<sup>16</sup>
  - Exerting multiple anti-aging effects (*Table*<sup>17</sup>). Metformin reduces several hallmarks of aging and may increase longevity.<sup>17</sup>
  - Lowering the risks of cancer, dementia, and mortality in patients with and without diabetes<sup>18</sup> due to its anti-aging effects. Scientists are actively studying metformin's anti-aging effects and trying to develop drugs with similar effects.
  - Counteracting inflammatory bowel disease, osteoporosis, neurodegeneration, inflammation, frailty, and senescence.<sup>19</sup>
- Metformin may sound like a wonder drug or panacea, but most of its multiple beneficial effects have been reported and replicated. Its therapeutic effects on obesity, diabetes, and dyslipidemia can prevent early mortality, but its anti-aging effects are also important and may help reduce premature mortality, which is common in psychiatric patients.<sup>20</sup> So, the question arises: At

some point, will metformin be used for persons not afflicted by diabetes or metabolic syndrome? For now, psychiatrists should continue to use it on label, but in the future, our patients may benefit from its “fringe benefits.”



**Henry A. Nasrallah, MD**  
Editor-in-Chief

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**Metformin's anti-aging effects may help reduce the premature mortality that is common in psychiatric patients**