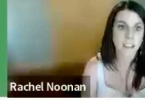
Compounded Metformin with Belmar



Metformin HCl / Naltrexone HCl / Oxytocin 100/8mg/100 IU Scored Tablet

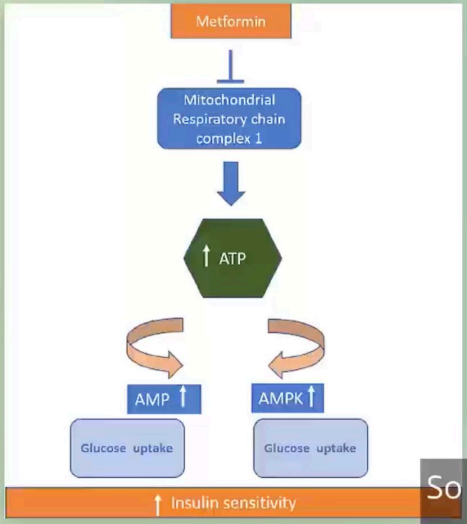
- Suggested dosing
  - 1 tablet by mouth twice daily
- Weight management benefit
  - Metformin
  - Naltrexone and oxytocin
    - May affect areas of the brain involved in appetite regulation
    - Can impact cravings, metabolism, energy

Topiramate ↑ metformin ↑ risk of lactic acidosis

Metformin Background

- Biguanide derived from the French lilac plant
- Mainstay medication for Type II DM
  - First-line therapy
  - Blood sugar reduction without risk of hypoglycemia
- Affordable and accessible
- Established safety profile spanning 60 years
- Multifaceted nature and the indications are growing

Metformin Mechanism of Action



- Metformin inhibits MC1 activating AMPK
- AMPK works as an energy sensor regulating metabolic pathways
  - Glucose and lipid metabolism
  - Energy homeostasis
- AMPK improves insulin sensitivity
  - Stimulates glucose uptake
  - Blocks hepatic gluconeogenesis
  - Encourages fatty acid oxidation

So metformin's primary

Metformin Side Effect Profile

Rachel Noonan

Potential Side Effects

- Gastrointestinal
  - Nausea, vomiting, diarrhea, dyspepsia, flatulence, abdominal pain
    - Transient and dose dependent
- Headache and loss of energy/strength
- B-12 deficiency

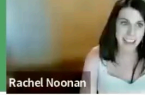
Pharmacokinetics

- Onset of action within days, up to 2 weeks for maximum effect
- Half-life: 4-9 hours plasma; 17-18 hours blood
- Peak effect with IR formulation: 2-3 hours

Metformin Black Box Warning – Lactic Acidosis

- **Description**
  - Metabolic condition resulting from overproduction of lactic acid
  - Lactic acid is a byproduct of cellular metabolism
- **Nonspecific symptoms**
  - General discomfort, muscle pain, respiratory distress, sleepiness, abdominal pain
- **Risk factors**
  - Kidney or liver impairment, hypoxic states, excessive alcohol use, being ≥65 years
  - Taking medications like topiramate (carbonic anhydrase inhibitors)
- **Contraindications**
  - Severe kidney dysfunction and metabolic acidosis

The Many Applications of Metformin



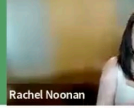
- Neurological Disease
- Diabetes
- Longevity
- CVD
- PCOS
- Weight Management
- Kidney Disease
- Cancer
- Liver Disease

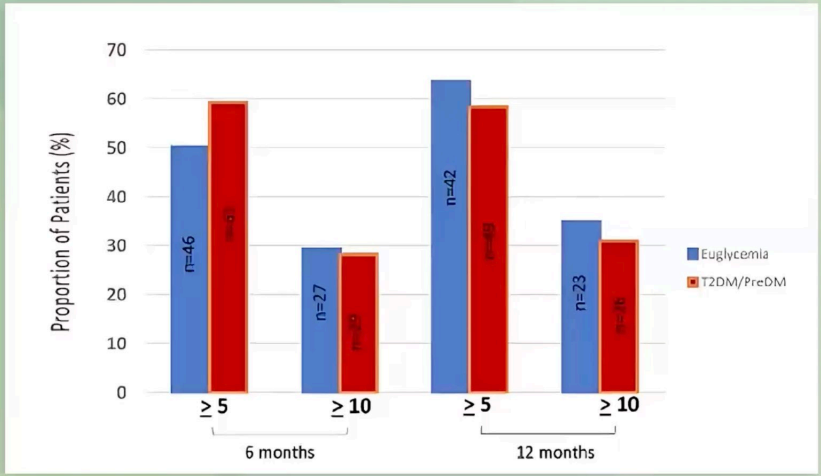
Metformin-Induced Weight Loss Study

Retrospective Cohort Study

- Patients received metformin as monotherapy for weight loss
  - Euglycemic (46% patients)
    - Average 1000 mg per day
  - T2DM/PreDM (54% patients)
    - Average 1500 mg per day
- Evaluated at 6- and/or 12-month follow-up

Metformin-Induced ≥5% or ≥10% Weight Loss





Metformin-Induced Weight Loss Study

Weight Loss Results

- At 6 months
  - Euglycemic: 6.5 +/- 6.0%
  - T2DM/PreDM: 6.5 +/- 6.1%
- At 12 months
  - Euglycemic: 7.4 +/- 6.2%
  - T2DM/PreDM: 7.3 +/- 7.7%

Metformin and Appetite

Metformin may have a dose-dependent effect on food intake

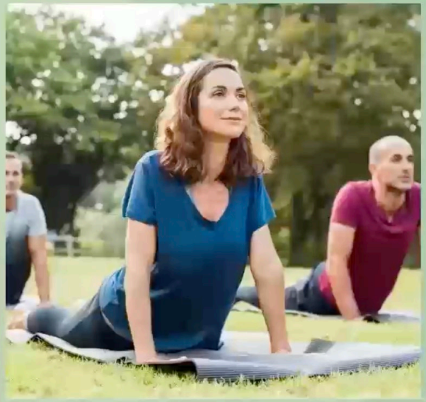
- Promotes increased lactate production after meals
  - Suppressing appetite
- Affects the food-reward relationship in the CNS
  - Induces metabolic changes in the brain
- Impacts the gut-brain axis
  - Increases the secretion of **GLP-1**
    - Appetite suppressing neuropeptide
  - Increases GDF15 blood levels, decreasing food intake

Metformin and the Gut Microbiome

Rachel Noonan

- Obese patients have different microbial flora
- Gut bacteria may play a role in developing metabolic syndrome or T2DM
- Short chain fatty acids (SCFA) are anti-inflammatory
  - Strengthen the intestinal barrier
  - Activate AMPK

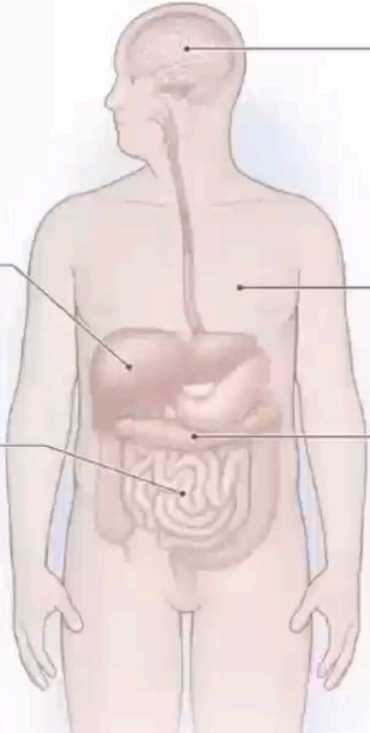
Metformin and the Gut Microbiome



- Introducing metformin to the GI tract appears to change gut bacteria
- Metformin promotes bacteria good at increasing SCFAs
  - Less hepatic gluconeogenesis
  - Less free fatty acid release from adipocytes

Rachel Noonan

Regulation of Obesity, Appetite, and Weight Loss by Metformin



CNS Effects:

- Suppression of orexigenic hypothalamic AgRP neurons via AMPK suppression
- Increase in hypothalamic leptin sensitivity
- Increased production of incretins and vagal signaling via NTS (GLP-1, PYY)
- Appetite suppression via post-prandial elevation in lactate production

Hepatic Effects:

- Decrease in hepatic glucose production and reduced systemic insulin requirement

Aging Effects:

- Reduction in sarcopenic obesity?
- Reversal of aging-related metabolic derangement

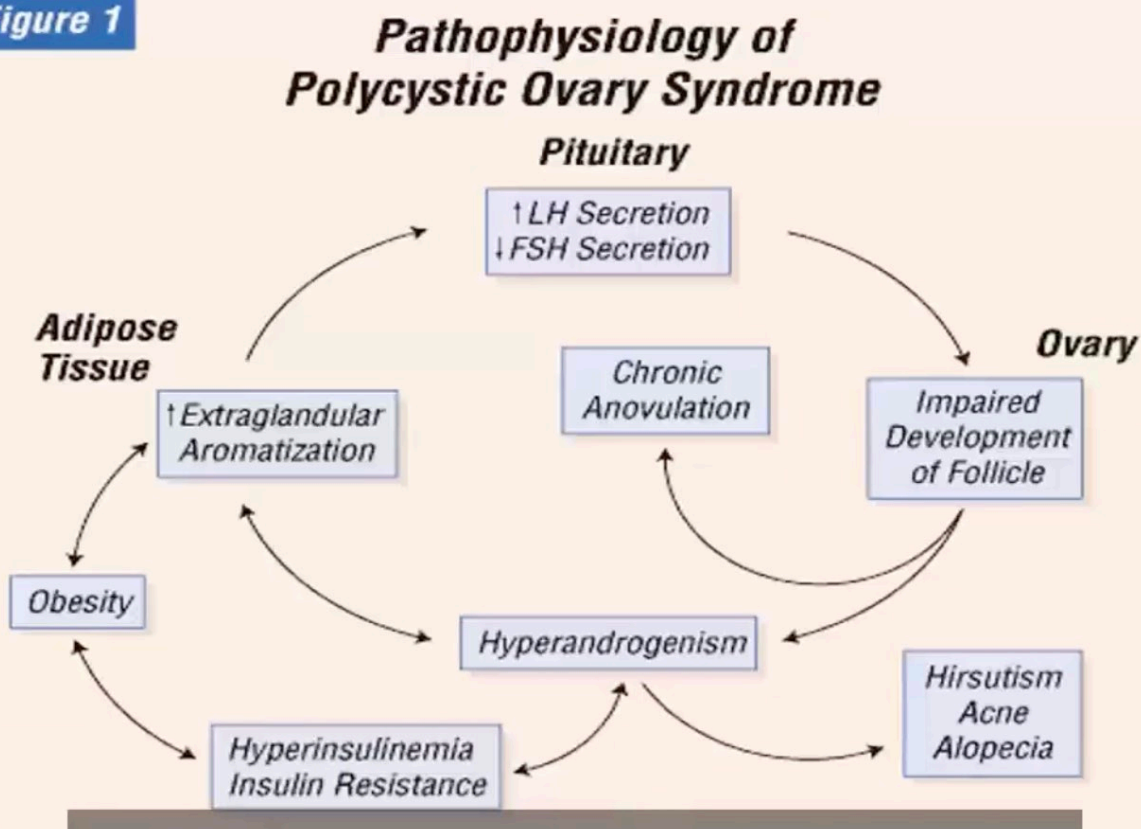
Gut Microbiome Effects:

- Alteration of gut microbiota (*Bacteroides/Firmicutes* ratio)
- Alteration in *Lactobacillus sp.* and hepatic glucose production
- Increase in *Ackermansia sp.*
- Increase in the production of SCFA

GI Effects:

- Nausea (central vs. GLP-1 mediated)
- Alteration in bile absorption and secondary gut hormone signaling
- Diarrhea and bloating due to altered enterocyte metabolism
- Dysgeusia

Figure 1



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and is that piece of it that leads to PCOS

Metformin and Longevity

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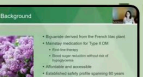
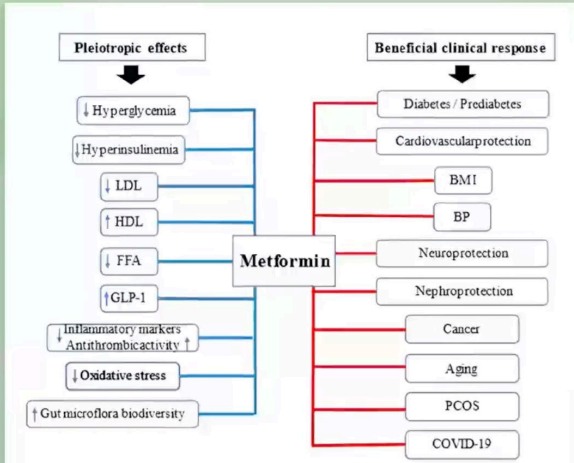
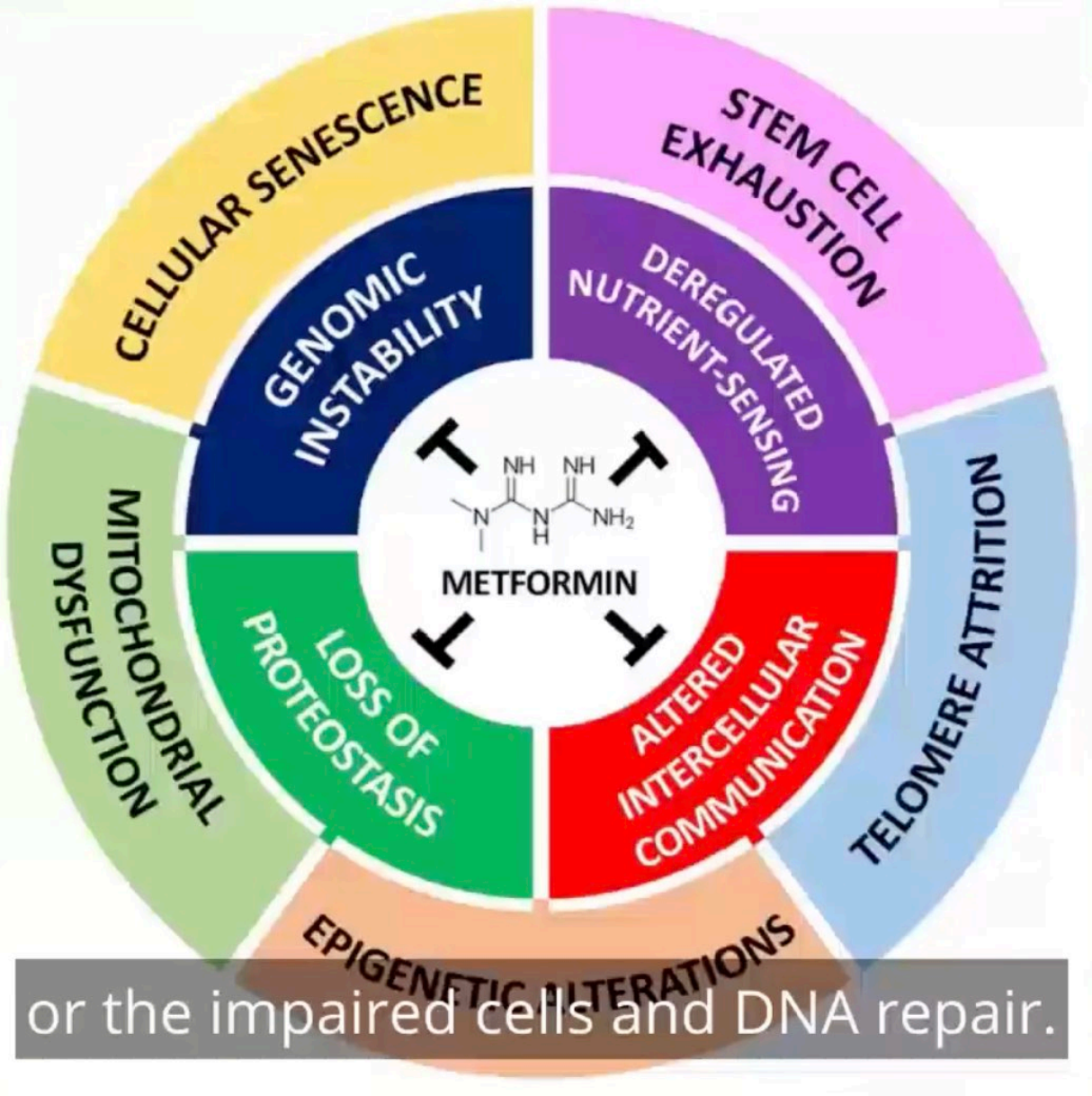
- Glucose metabolism regulation
- Protective effect on cellular processes
  - DNA damage and ROS
  - Inflammation
  - Oxidative stress and apoptosis
  - Cell senescence

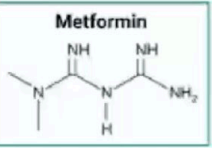






or the impaired cells and DNA repair.

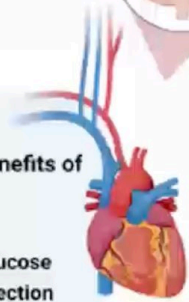
Metformin



Galega officinalis

Cardiovascular benefits of metformin

- Lowered blood glucose
- Endothelium protection
- Antioxidative actions
- ↓inflammation
- ↓leukocyte adhesion
- ↓blood pressure
- ↓micro/macrovascular complications

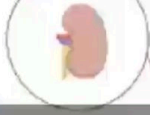


- Metabolic, CV and anti-inflammatory actions decrease neurodegenerative disease.
- Antihyperglycemic-independent effects elicit GDF15-mediated weight loss.

- Lipid homeostasis
- ↓adiposity

- ↓gluconeogenesis and lipogenesis

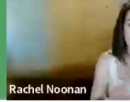
- AMPK-dependent GLP-1 release
- Enhanced SGLT-1 activity?
- GI side effects
- ↓vitamin B12 absorption



- Secretion via MATE/OCT transporters
- ↓GFR leading to metformin accumulation and toxicity/lactic acidosis

will die of cardiovascular disease

Metformin and Longevity



- Animal studies support promising future for metformin
  - Potential for extended disease-free lifespan
  - Evident in roundworm (C. elegans) and mice
- Meta-analysis involving 53 studies investigated metformin's geroprotective effect in humans
  - Reductions in all-cause mortality and age-related diseases
- Longevity mechanisms and targets are under research
  - No shortage of proposed theories

The TAME Trial

Targeting Aging with Metformin (TAME) Trial:

- Series of nationwide six-year clinical trials across 14 research institutions
- Involving over 3,000 patients between 65-79
- Focused on the idea that aging can be addressed with medication like other disease states

The TAME Trial

Study Design and Goal

- Patients will receive metformin 1500 mg/day for 6 years with a 3.5 year follow-up period
- The aim is to help achieve aging as an indication for metformin
- Still raising funds for launch