

PRECISION METABOLISM SUPPORT PROGRAM

Metformin ER · Berberine · Custom-Compounded · AMPK Activation
Prescriber Reference Guide · The Medicine Shoppe, York PA

Insulin Resistance · Prediabetes · Metabolic Syndrome · Blood Sugar Regulation · Lipid Support · Rx Required

Program Overview

Insulin resistance, prediabetes, and metabolic syndrome represent a continuum of cardiometabolic dysfunction affecting an estimated 88 million Americans. Standard commercial treatment options -- primarily fixed-dose metformin tablets -- lack the flexibility for the individualized dosing that optimal metabolic management requires, particularly during titration, in patients with GI intolerance, or when low-dose or non-standard strengths are clinically indicated. This program offers compounded metformin extended-release (ER) capsules and pharmaceutical-grade berberine at prescriber-specified doses, enabling a precision approach to metabolic therapy with clean formulations and exact dose control.

Key Clinical Advantages

- Custom dose precision -- metformin ER in any strength, including doses unavailable commercially (e.g., 250 mg, 375 mg, 750 mg ER); eliminates the need to split or approximate with commercial tablets
- Extended-release formulation -- reduces GI side effects (nausea, diarrhea) that drive metformin discontinuation in 20-30% of patients on IR formulations; compounded ER capsules provide controlled release profile
- Pharmaceutical-grade berberine -- standardized purity and exact dosing unlike variable-potency supplements; enables precise titration and combination with metformin ER
- Dual AMPK activation -- metformin and berberine activate AMPK through complementary pathways, providing additive metabolic benefit; useful when metformin alone is insufficient or when a natural adjunct is preferred
- Clean capsules -- no dyes, no unnecessary fillers; excipient-free options available for sensitive patients; gelatin or HPMC shell per preference
- Non-controlled -- no DEA scheduling; straightforward prescribing; cash pay with no prior authorization burden

Metabolic Pathophysiology

Understanding the pathophysiology of insulin resistance and metabolic syndrome clarifies why dual AMPK-activating therapy with metformin ER and berberine provides mechanistically complementary benefit.

Insulin Resistance

A state in which target tissues (skeletal muscle, liver, adipose) respond inadequately to insulin signaling. Results in compensatory hyperinsulinemia as the pancreas attempts to maintain euglycemia. The primary driver of prediabetes, T2DM progression, metabolic syndrome, NAFLD, PCOS, and cardiovascular risk.

AMPK (AMP-activated Protein Kinase)

The cell's metabolic master switch -- activated by energy deficit (high AMP:ATP ratio) and by pharmacological agents including metformin and berberine. AMPK

Hepatic Glucose Output	<p>activation enhances glucose uptake, inhibits hepatic gluconeogenesis, promotes fatty acid oxidation, reduces lipogenesis, and improves mitochondrial biogenesis. It is the primary molecular target of this program.</p> <p>The liver produces glucose continuously via gluconeogenesis and glycogenolysis. In insulin resistance, this hepatic glucose output is inappropriately elevated even in the fed state -- a major driver of fasting hyperglycemia. Both metformin and berberine suppress hepatic gluconeogenesis via AMPK and complementary pathways.</p>
Skeletal Muscle Glucose Uptake	<p>Skeletal muscle accounts for ~80% of post-meal glucose disposal. In insulin resistance, GLUT4 translocation to the muscle cell surface is impaired, reducing glucose uptake. AMPK activation by metformin and berberine promotes GLUT4 translocation independently of insulin, improving post-meal glucose clearance.</p>
Mitochondrial Dysfunction	<p>Impaired mitochondrial oxidative phosphorylation in insulin-resistant tissues contributes to lipid accumulation, ROS generation, and inflammatory signaling that perpetuate insulin resistance. Metformin (complex I inhibition) and berberine (mitochondrial effects) both modulate mitochondrial function as part of their AMPK-activating mechanisms.</p>
Metabolic Syndrome	<p>Cluster of insulin resistance-related cardiometabolic risk factors: central obesity, elevated fasting glucose, hypertriglyceridemia, low HDL, and hypertension. Both metformin and berberine have evidence for addressing multiple components of metabolic syndrome simultaneously.</p>

Metformin ER -- Mechanism, Evidence & Compounding Rationale

Mechanism of Action

Primary: Hepatic Gluconeogenesis Inhibition	<p>Metformin inhibits mitochondrial complex I (NADH dehydrogenase) in hepatocytes, reducing mitochondrial energy production and increasing the AMP:ATP ratio. This activates AMPK, which phosphorylates and inhibits key gluconeogenic enzymes (PEPCK, G6Pase), reducing hepatic glucose output. Fasting glucose reduction is the primary clinical effect.</p>
AMPK Activation	<p>Metformin activates AMPK both directly (via complex I inhibition) and through upstream kinases (LKB1). AMPK activation improves insulin sensitivity in muscle and liver, reduces lipogenesis, promotes fatty acid oxidation, and suppresses mTOR-driven inflammatory signaling.</p>
GLP-1 Enhancement	<p>Recent research has identified a gut-mediated mechanism -- metformin increases GLP-1 secretion from intestinal L-cells, contributing to glucose-lowering and appetite modulation effects independent of AMPK. This mechanism is particularly relevant to the ER formulation (greater distal gut exposure).</p>
Gut Microbiome Modulation	<p>Metformin alters the gut microbiome -- increasing short-chain fatty acid-producing bacteria and reducing pathogenic species. Microbiome changes may contribute to metformin's metabolic effects and may be enhanced with ER formulation's prolonged gut exposure.</p>
Weight Neutrality / Modest Loss	<p>Unlike sulfonylureas and insulin, metformin does not cause weight gain and may modestly support weight loss, particularly in conjunction with lifestyle modification. Mechanism includes appetite modulation via GLP-1 and reduced hepatic lipogenesis.</p>

ER vs. IR: Why Extended-Release Matters

GI Tolerability	The most common barrier to metformin adherence is GI side effects -- nausea, diarrhea, and abdominal cramping -- occurring in 20-30% of patients on immediate-release (IR) and driving discontinuation in a significant subset. ER formulation reduces peak drug concentration in the proximal GI tract, substantially improving GI tolerability. Multiple RCTs confirm metformin ER has significantly fewer GI side effects than IR at equivalent doses.
Release Mechanism	Compounded metformin ER uses a hydrophilic matrix system that controls drug release over 8-12 hours. Slower absorption results in lower peak plasma concentrations, reduced proximal gut drug levels (primary site of GI side effects), and greater distal gut exposure (relevant for GLP-1 and microbiome mechanisms).
Dosing Frequency	ER allows once-daily or twice-daily dosing vs. IR's typical three-times-daily schedule, improving adherence and simplifying regimens.
Commercial ER Limitations	Commercial metformin ER tablets are available in 500 mg and 750 mg (Glucophage XR) and 500 mg, 750 mg, 1000 mg (generics). Doses outside these strengths -- 250 mg (for ultra-sensitive titration), 375 mg, 625 mg, or any custom strength -- require compounding. Patients who need low starting doses for tolerability, or mid-range titration doses, cannot access these commercially.
Compounding Advantage	Compounded metformin ER capsules provide the ER release profile at any prescriber-specified dose. This is particularly valuable for: initiating at very low doses (250 mg) in GI-sensitive patients; mid-range titration steps (375 mg, 625 mg); patients who need doses between commercial strengths; and combination capsules with berberine.

Evidence Base

T2DM & Prediabetes	Metformin is the first-line pharmacological agent for type 2 diabetes in virtually all major guidelines (ADA, AACE, EASD). The Diabetes Prevention Program (DPP) demonstrated metformin reduced progression from prediabetes to T2DM by 31% vs. placebo (lifestyle intervention reduced by 58%). Strong evidence for long-term cardiovascular benefit (UKPDS).
Insulin Resistance (Non-Diabetic)	Metformin is widely used off-label for insulin resistance, metabolic syndrome, PCOS, and prediabetes. ADA Standards of Care recommend metformin for prediabetes, particularly in patients with BMI >35, age <60, or women with prior GDM.
PCOS	Metformin is a cornerstone of PCOS management -- improves insulin sensitivity, reduces androgen levels, restores menstrual regularity, and supports ovulation. Used in combination with lifestyle intervention and, when indicated, other hormonal therapies.
Longevity & Anti-Aging	Emerging evidence (TAME trial ongoing) supports metformin as a potential anti-aging intervention -- epidemiological data suggest metformin users have lower rates of cancer, cardiovascular disease, and all-cause mortality than age-matched non-users. Mechanism: AMPK activation, mTOR inhibition, inflammatory pathway suppression.
Safety Profile	Metformin has an outstanding long-term safety record across decades of use. Lactic acidosis, the historically cited concern, is extremely rare at appropriate doses in patients without contraindications (eGFR <30, significant hepatic impairment, acute illness with hemodynamic compromise). No hypoglycemia risk as monotherapy.

Berberine -- Mechanism, Evidence & Compounding Rationale

What Is Berberine

Berberine is an isoquinoline alkaloid found in several medicinal plants including *Berberis vulgaris* (barberry), *Berberis aristata* (Indian barberry), *Coptis chinensis* (goldenseal), and *Hydrastis canadensis*. It has been used in traditional Chinese and Ayurvedic medicine for centuries and has been the subject of substantial modern clinical research for metabolic, cardiovascular, and antimicrobial applications. Compounded berberine capsules provide pharmaceutical-grade standardized purity and exact dose precision unavailable with OTC supplement-grade products.

Mechanism of Action

AMPK Activation (Primary)	Berberine activates AMPK through a mechanism partly distinct from metformin -- primarily via inhibition of mitochondrial complex I and through upstream activation via SIRT1 and CaMKK2 pathways. The complementary AMPK activation pathways of berberine and metformin provide rationale for combination use.
Hepatic Gluconeogenesis	AMPK-mediated inhibition of PEPCK and G6Pase expression reduces hepatic glucose output -- the same end-point as metformin, via overlapping but not identical upstream signaling. Both agents suppress fasting glucose through this shared mechanism.
GLUT4 Upregulation	Berberine increases GLUT4 expression and translocation in skeletal muscle and adipose tissue, improving peripheral glucose uptake. Evidence suggests berberine may have additive or synergistic effects with metformin on GLUT4-mediated glucose disposal.
Incretin Enhancement	Berberine increases GLP-1 secretion from intestinal L-cells -- a mechanism shared with metformin ER. Additive GLP-1-enhancing effects with combination therapy may contribute to appetite modulation and postprandial glucose control.
Lipid Regulation	Berberine activates the LDLR (LDL receptor) gene through a PCSK9-independent mechanism, increasing LDL receptor expression and hepatic LDL clearance. Reduces LDL cholesterol, total cholesterol, and triglycerides. This lipid-modulating activity is notably more pronounced than metformin's modest lipid effects.
Gut Microbiome	Berberine has significant effects on the gut microbiome -- reduces pathogenic bacteria, increases beneficial species including <i>Akkermansia muciniphila</i> , and modulates the gut-liver axis. Microbiome modulation contributes to metabolic benefits and may be additive with metformin's microbiome effects.
Anti-Inflammatory	Berberine inhibits NF-κB, reduces TNF-alpha and IL-6, and suppresses NLRP3 inflammasome activation -- addressing the chronic low-grade inflammation that perpetuates insulin resistance and metabolic syndrome.

Evidence Base

Blood Sugar & T2DM	Multiple RCTs have compared berberine to metformin in T2DM. Zhang et al. (2008) demonstrated berberine 500 mg three times daily achieved HbA1c and fasting glucose reductions comparable to metformin 500 mg three times daily at 3 months. Yin et al. (2008) confirmed similar findings. Meta-analyses of 27+ RCTs support berberine's significant blood sugar lowering effects.
Lipid Regulation	Multiple RCTs demonstrate berberine reduces total cholesterol by ~0.61 mmol/L, LDL by ~0.65 mmol/L, and triglycerides by ~0.50 mmol/L. Effect size is clinically meaningful -- comparable to low-dose statin therapy for LDL reduction in some studies. This lipid benefit is additive to metformin.
PCOS	Several RCTs support berberine in PCOS -- comparable to metformin for insulin sensitivity, testosterone reduction, and menstrual cycle regulation. One head-to-head RCT (Li et al.) found berberine outperformed metformin on several PCOS endpoints.
Metabolic Syndrome	Clinical trials support berberine for multiple components of metabolic syndrome - - fasting glucose, triglycerides, waist circumference, and blood pressure -- addressing the full cardiometabolic risk cluster.
Combination with Metformin	Pilot studies and clinical series suggest additive benefit when berberine is combined with metformin -- improvement in glycemic control beyond either agent alone. Mechanistic rationale is strong (complementary AMPK pathways, additive gut microbiome effects, berberine's lipid benefits filling a gap in metformin's profile).
Safety Profile	Berberine is generally well-tolerated. GI side effects (nausea, constipation, diarrhea) are the most common adverse effects -- generally mild and dose-dependent. No significant hepatotoxicity or serious adverse events in clinical trials at standard doses. Not recommended in pregnancy (uterine stimulation in animal models).

Metformin vs. Berberine vs. Combination -- Comparative Profile

	Metformin ER	Berberine	Combination
Primary AMPK Pathway	Complex I inhibition / LKB1	Complex I + SIRT1 / CaMKK2	Complementary dual activation
Fasting Glucose	Strong reduction	Comparable to metformin	Additive benefit
Post-Meal Glucose	Moderate improvement	Good improvement (GLUT4)	Enhanced GLUT4 + GLP-1
LDL Cholesterol	Minimal effect	Significant reduction (~0.65 mmol/L)	Additive lipid benefit
Triglycerides	Modest reduction	Meaningful reduction	Enhanced effect
GLP-1 Enhancement	Yes (gut mechanism)	Yes (gut mechanism)	Potentially additive
Gut Microbiome	Positive modulation	Positive modulation	Additive
Anti-Inflammatory	Moderate	Strong (NF-kB, NLRP3)	Enhanced
Regulatory Status	FDA-approved Rx	OTC supplement / compounded Rx	Rx compounded combination

GI Side Effects	Reduced with ER formulation	Mild, dose-dependent	Monitor; start low
Pregnancy	Contraindicated in T1DM; use in GDM per guidelines	Not recommended	Not recommended
Hypoglycemia Risk	None as monotherapy	None as monotherapy	None as monotherapy

Patient Selection & Indications

Appropriate Candidates

- Prediabetes (IFG: fasting glucose 100-125 mg/dL; IGT: 2-hr OGTT 140-199 mg/dL; HbA1c 5.7-6.4%) -- metformin is ADA-recommended in this population, especially with BMI >35, age <60, or prior GDM
- Insulin resistance without frank hyperglycemia -- HOMA-IR >2.5, fasting insulin elevation, clinical features of IR (acanthosis nigricans, central obesity, hypertriglyceridemia with low HDL)
- Metabolic syndrome (3+ of: waist >40" men / >35" women, triglycerides >150, HDL <40 men / <50 women, BP >130/85, fasting glucose >100)
- PCOS -- metformin is guideline-recommended; berberine has additional evidence for androgen reduction and cycle regulation
- Patients on commercial metformin IR with GI intolerance -- compounded ER provides the same active ingredient with significantly better tolerability
- Patients needing doses not commercially available -- 250 mg for ultra-slow titration, 375 mg, 625 mg, or any custom strength
- Patients seeking a natural metabolic adjunct -- berberine as complement to metformin or as standalone for patients preferring a plant-derived agent with robust clinical evidence
- Longevity / healthspan optimization protocols -- metformin's emerging anti-aging evidence makes it increasingly used in this context in appropriate patients

Contraindications & Cautions

Metformin -- Renal Function	Contraindicated when eGFR <30 mL/min/1.73m ² . Use with caution eGFR 30-45 (reduce dose, monitor more frequently). Check eGFR before initiating and annually (or with any acute illness or medication change that could affect renal function).
Metformin -- Hepatic	Significant hepatic impairment -- avoid metformin (impaired lactate clearance increases lactic acidosis risk). ALT/AST >3x ULN is a general threshold for caution; discuss risk-benefit.
Metformin -- Contrast Media	Hold metformin 48 hours before and after iodinated contrast media administration for patients with eGFR <60 or undergoing procedures with risk of acute kidney injury.
Metformin -- B12 Deficiency	Metformin reduces vitamin B12 absorption in ~10-30% of long-term users via calcium-dependent ileal membrane antagonism. Check B12 annually in patients on long-term metformin; supplement if low-normal or deficient.
Berberine -- Drug Interactions	Berberine is a CYP3A4, CYP2D6, and CYP2C9 inhibitor. Clinically significant interactions: cyclosporine (increased levels), metoprolol/other beta-blockers (increased levels), warfarin (increased INR -- monitor), certain statins (increased exposure -- monitor for myopathy). Review full medication list before prescribing.

Berberine -- Pregnancy	Not recommended in pregnancy -- animal studies suggest uterine-stimulating effects; insufficient human safety data. Discontinue before attempting conception.
Combination GI Effects	When combining metformin ER and berberine, start each at a low dose and titrate independently; both have GI side effects that are additive if introduced too rapidly simultaneously.

Dosing & Titration Protocols

Metformin ER

Starting Dose	250-500 mg once daily with the evening meal; starting at 250 mg compounded ER is preferred for GI-sensitive patients, elderly patients, or those with prior IR metformin intolerance
Titration	Increase by 250-500 mg every 1-2 weeks as tolerated; most patients reach maintenance at 1000-2000 mg/day; dose adjustments guided by tolerability and glycemic response
Maintenance Range	500-2000 mg/day in one or two divided doses; maximum 2550 mg/day (though most benefit achieved by 2000 mg)
Administration	Take with meals to reduce GI side effects; evening meal administration preferred for once-daily dosing (aligns with overnight hepatic glucose output suppression)
Custom Doses Available	250 mg, 375 mg, 500 mg, 625 mg, 750 mg, 1000 mg, or any custom strength; titration packs available (multiple strengths in one order) for structured titration protocols
eGFR Dose Adjustment	eGFR 45-60: proceed with standard dosing, monitor more frequently; eGFR 30-45: reduce to 50% of standard dose, use with caution; eGFR <30: contraindicated

Berberine

Starting Dose	250-500 mg once or twice daily with meals; start at 250 mg twice daily in GI-sensitive patients
Titration	Increase to 500 mg twice daily after 1-2 weeks if tolerated; target dose 500 mg twice or three times daily (1000-1500 mg/day)
Maintenance Range	500-1500 mg/day in 2-3 divided doses with meals; divided dosing reduces peak GI effects and matches the shorter half-life of berberine
Administration	With meals; divided dosing improves tolerability and maintains more consistent plasma levels; avoid taking with large amounts of dietary fiber concurrently (may reduce absorption)
Available Strengths	250 mg, 500 mg standard; any custom strength on request

Combination Protocol

Sequencing	Initiate metformin ER first at low dose and titrate to tolerance; add berberine after 2-4 weeks once metformin is established; avoids compounding GI effects of simultaneous initiation
Combination Capsules	Metformin ER + berberine in a single capsule available on request; specify both doses; useful for maintenance dosing once both agents are individually titrated to target doses
Monitoring Frequency	Check fasting glucose and HbA1c at baseline, 3 months, and 6 months after reaching maintenance dose; lipid panel at baseline and 6 months (berberine's lipid effects)
Dose Adjustment	Adjust doses independently based on glycemic response, lipid response, and tolerability; combination therapy may achieve metabolic goals at lower individual doses of each agent

Drug Interactions

Berberine + Warfarin	Berberine inhibits CYP2C9, increasing warfarin exposure. Monitor INR closely when initiating, adjusting dose, or discontinuing berberine in patients on warfarin. Warfarin dose adjustment may be needed.
Berberine + Cyclosporine	Berberine inhibits CYP3A4, significantly increasing cyclosporine blood levels. Avoid combination or monitor cyclosporine trough levels extremely closely.
Berberine + Statins	CYP3A4 inhibition increases simvastatin and lovastatin exposure (higher myopathy risk); less effect on pravastatin, rosuvastatin, or fluvastatin. Prefer non-CYP3A4-metabolized statins when combining with berberine; monitor for myopathy.
Berberine + Antidiabetic Agents	Additive blood glucose lowering with metformin, sulfonylureas, GLP-1 agonists, and insulin. Monitor for hypoglycemia when adding berberine to existing antidiabetic regimens, particularly with insulin or sulfonylureas.
Metformin + Contrast	Hold metformin (including compounded ER) 48 hours before and after iodinated contrast in patients with eGFR <60 or undergoing high-risk procedures; resume when renal function confirmed stable.
Metformin + Alcohol	Heavy alcohol use with metformin increases lactic acidosis risk (alcohol inhibits hepatic lactate clearance). Counsel patients to limit alcohol; avoid in heavy drinkers or those with liver disease.
Metformin + Cationic Drugs	Some cationic drugs (cimetidine, trimethoprim, vancomycin) compete with metformin for renal tubular secretion, potentially increasing metformin levels. Monitor with concurrent use of these agents, particularly in patients with reduced renal function.

Monitoring & Follow-Up

Baseline	Fasting glucose, HbA1c, fasting insulin, HOMA-IR (calculated); lipid panel; CMP (renal and hepatic function); eGFR; B12 (if adding metformin); medication reconciliation for CYP interactions (berberine); weight and waist circumference
6-8 Weeks	Assess GI tolerability; fasting glucose; dose adjustment as needed; check INR if on warfarin and berberine added
3 Months	HbA1c, fasting glucose, fasting insulin; lipid panel (berberine lipid effect); weight; assess whether dose targets are met; titrate as needed
6 Months	Full metabolic panel; HbA1c target assessment; lipid response to berberine; renal function (eGFR) and B12 for metformin
Annual	B12 level in all patients on long-term metformin; bone density consideration (some data on metformin and bone); reassess eGFR; lipid panel; HbA1c; weight trajectory; reassess indication and dose
Hypoglycemia Awareness	As monotherapy or dual therapy without insulin/sulfonylureas, neither metformin nor berberine causes hypoglycemia. Counsel patients that symptoms are not expected; if hypoglycemia occurs, evaluate for concurrent hypoglycemic agents or adrenal insufficiency.

Formulation & Dispensing

Metformin ER Form	Extended-release oral capsules; hydrophilic matrix release system; compounded at The Medicine Shoppe from USP pharmaceutical-grade metformin HCl
Berberine Form	Immediate-release oral capsules; compounded from pharmaceutical-grade berberine HCl with standardized purity
Available Strengths	Metformin ER: 250 mg, 375 mg, 500 mg, 625 mg, 750 mg, 1000 mg, any custom strength. Berberine: 250 mg, 500 mg, any custom strength
Combination Capsules	Metformin ER + berberine in a single capsule available at maintenance doses; specify both strengths; compatibility confirmed
Capsule Shell	Gelatin (standard) or HPMC (vegan) -- specify on prescription
Excipients	No dyes, no unnecessary fillers; MCC only as needed; excipient-free options for highly sensitive patients
Quantity	30-day supply standard; 90-day available; titration packs (multiple strengths) available for structured initiation protocols
Pricing	Cash pay -- contact pharmacy for current pricing
BUD / Storage	Per USP compounding standards; room temperature; labeled on each preparation

Ordering & Contact Information

All preparations require a valid prescription specifying compound(s), dose(s), quantity, and dosing instructions. The compounding pharmacist is available to discuss titration pack options and combination capsule specifications.

How to Order

- By phone -- call (717) 846-0500; ask for the compounding pharmacist; have patient name, DOB, compound(s), dose(s), quantity, and any titration pack or combination capsule request ready
- By fax -- send prescription to (717) 845-8767; specify compound name and ER designation, dose, quantity, and sig; note capsule shell (gelatin or HPMC) and any excipient restrictions
- E-prescribe -- select 'Compound' as medication type; enter in Sig/Comments (e.g., 'Metformin ER 500 mg capsule -- take 1 capsule with evening meal daily; qty 30' or 'Berberine HCl 500 mg capsule -- take 1 capsule twice daily with meals; qty 60')

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