RESEARCH PAPER | REVISION 1 | PREPRINT

Four-Agent Adipose and Energy Modulation: Evidence, Translational Limits, and Interaction Risk

A bounded mechanistic analysis of yohimbine, clenbuterol, retatrutide, and 5-Amino-1MQ

Critical mechanistic evidence map and interaction-risk hypothesis paper

Not a treatment protocol. Not a clinical recommendation. Not evidence of combination synergy.

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Evidence cutoff: 30 July 2026

Status: Preprint; not peer reviewed

A bounded analysis of four unequal evidence objects and the experiments required before any interaction claim.

Evidence boundary

This paper is a research synthesis, not a treatment protocol. It does not recommend, prescribe, optimize, or validate the use of yohimbine, clenbuterol, retatrutide, 5-Amino-1MQ, or any combination of them. It supplies no dose, titration, cycle, meal-timing, exercise-timing, compounding, sourcing, or administration instruction. No controlled human study of the four-agent combination was identified through the evidence cutoff. No claim of clinical safety, compatibility, additive benefit, synergy, or superiority is made.

Retatrutide remained investigational and was not approved by any regulatory agency through the evidence cutoff. The US Food and Drug Administration states that retatrutide cannot lawfully be used in compounding and has not been found safe and effective for any condition [27]. Clenbuterol is not an ingredient of an FDA-approved human drug in the United States and is prohibited in sport under the 2026 World Anti-Doping Agency list [14,39]. Published human pharmacokinetic, safety, or efficacy data for 5-Amino-1MQ were not identified. The distinction between a named chemical, a verified research material, and an unregulated product is therefore material to every inference in this paper.

Abstract

Four agents are frequently joined in informal body-composition narratives because they affect different parts of energy intake, adrenergic signaling, adipose lipid mobilization, or nicotinamide metabolism. That apparent pathway coverage does not establish that the agents are compatible, that their effects persist on the same time scale, or that their combination improves fat loss. This paper adversarially evaluates yohimbine, clenbuterol, retatrutide, and 5-Amino-1MQ at the level of material identity, target pharmacology, acute biomarkers, sustained human outcomes, preclinical findings, regulatory state, and interaction risk.

The evidence is sharply asymmetric. Retatrutide has randomized human trials showing substantial body-weight and fat-mass reduction in studied populations, while remaining investigational. Yohimbine has small and heterogeneous human studies, including acute evidence of increased glycerol and non-esterified fatty acids under fasting conditions, but weak evidence for sustained body-composition efficacy. Clenbuterol has acute human metabolic effects, yet longer-duration randomized studies do not support a dependable fat-loss effect and report increased heart rate, reduced cardiorespiratory fitness, reduced muscle oxidative capacity, or signaling tolerance. 5-Amino-1MQ has compound-specific cell and mouse evidence, but no published human pharmacology was identified.

No pairwise or four-agent efficacy, pharmacokinetic-interaction, or safety trial was identified. The literature therefore supports mechanistic hypotheses, not demonstrated synergy. The strongest cross-agent signal is not an efficacy signal but a potential hazard convergence: yohimbine and clenbuterol can both increase sympathetic or cardiovascular stress, while retatrutide has produced dose-dependent heart-rate increases in clinical trials. A formal framework is presented for adipose lipid balance, dynamic energy balance, fixed-dose interaction contrasts, response surfaces, exposure, and time-varying hazard.

The paper concludes with a falsifiable validation sequence that requires verified materials, single-agent exposure-response data, pairwise safety gates, and a complete factorial design before any four-agent interaction claim.

Keywords: adipose tissue; body composition; clenbuterol; evidence map; interaction; lipolysis; NNMT; retatrutide; synergy; yohimbine; 5-Amino-1MQ

Plain-language summary

The source manuscript described four compounds as a coordinated fat-loss protocol. The current evidence does not justify that description.

- Retatrutide has the strongest human evidence for weight and fat-mass reduction, but it is still investigational.
- Yohimbine can acutely increase markers of fat mobilization in selected fasting conditions. That does not prove durable or regional fat loss.
- Clenbuterol can acutely increase energy expenditure and fat oxidation, but longer human studies found no fat-mass reduction and identified important performance and cardiovascular costs.
- 5-Amino-1MQ has promising cell and mouse findings. Human exposure, efficacy, safety, and interaction data were not identified.
- No controlled study has tested the four agents together.

The scientifically defensible conclusion is that the four-agent concept is an unvalidated interaction hypothesis with substantial safety and translational uncertainty. It is not an evidence-based protocol.

1. Research question and rationale

The relevant question is not whether each agent can be connected to a favorable pathway term. The relevant question is:

> In a defined biological system and exposure range, does a verified combination alter a prespecified body-composition or metabolic endpoint beyond a prespecified noninteraction model, with acceptable uncertainty and without failure of cardiovascular, metabolic, behavioral, or material-quality guardrails?

That question contains requirements absent from the source manuscript. It requires defined materials, comparable outcomes, a declared null model, a complete set of control conditions, time-resolved exposure, and a safety analysis. A pathway diagram alone cannot answer it.

The source manuscript made four recurring inference errors:

1. It treated acute lipolysis or substrate oxidation as sustained fat-mass loss.
2. It transferred cell and mouse findings into human outcome predictions.

3. It called mechanistic complementarity "synergy" without combination data or a noninteraction model.
4. It converted pharmacokinetic descriptions into timing and cycling instructions despite absent combination pharmacology.

Revision 1 retains the underlying scientific question while removing the protocol structure and subjecting each proposed relation to a claim-level evidence standard.

2. Methods

2.1 Review design

This paper is a curated, adversarial mechanistic evidence map. It is not a systematic review, does not claim exhaustive retrieval, and does not estimate pooled efficacy. Searches were updated through 30 July 2026 in PubMed, PubMed Central, ClinicalTrials.gov, regulator and sponsor records, and citation chains from pivotal primary studies. Search concepts combined each agent name and identifier with terms for pharmacokinetics, target engagement, lipolysis, energy expenditure, body composition, obesity, safety, toxicity, heart rate, interaction, and combination.

Priority was given to:

1. randomized controlled human studies;
2. prospective human pharmacokinetic or pharmacodynamic studies;
3. trial registries and regulator records;
4. compound-specific animal and cell experiments;
5. target-biology experiments;
6. methodological literature for interaction analysis.

Reviews were used only for orientation when a primary source could not carry the same claim. Company disclosures were retained only for current development status or explicitly labeled topline results. Vendor pages, clinics, newsletters, bodybuilding sources, social media, and anecdotes were excluded as biological evidence.

2.2 Evidence labels

Each proposition receives one of four labels:

Label	Meaning
Observed	A bounded result reported in the cited system, preserving population, design, endpoint, and duration.
Inferred	An interpretation supported by the observed result but not directly measured.

Label	Meaning
Hypothesized	A biologically motivated relation for which the stated experiment has not been performed.
Unknown	Evidence is absent, inadequate, contradictory, or not transferable to the proposed context.

The labels apply to individual propositions, not entire compounds. "Observed" means reported by the cited study, not independently observed by the author.

2.3 Evidence hierarchy and translational distance

Evidence was not collapsed into a numeric score. Each claim was instead assessed across:

- material identity and analytical verification;
- experimental system;
- design and control condition;
- sample size and duration;
- proximal versus distal endpoint;
- exposure plausibility;
- independent replication;
- direction and precision of effect;
- conflict or null evidence;
- regulatory and product-status relevance.

A human randomized fat-mass endpoint and a mouse adipocyte marker are not two estimates of the same quantity. They occupy different evidentiary layers.

2.4 Interaction terminology

Mechanistic complementarity means that two perturbations plausibly affect different processes in a shared causal graph. Additivity means that a measured combination follows a declared noninteraction model. Synergy means that the measured combination departs from that prespecified model in a reproducible direction and region of dose, exposure, and time. Because different null models answer different questions, "synergy" has no model-free coefficient [35-38].

No controlled pairwise or four-agent combination study was identified. This paper therefore uses "interaction hypothesis" unless a method is being defined.

2.5 Search limitations

The evidence base includes small studies, sponsor-funded studies, short interventions, incomplete publication of current phase 3 obesity results, and sparse human data for yohimbine and clenbuterol. The

search cannot prove that an unpublished study does not exist. "Not identified" is therefore used instead of "does not exist." The evidence cutoff is also important: sponsor topline releases available by 30 July 2026 are not equivalent to peer-reviewed reports.

3. Material identity, status, and evidence asymmetry

3.1 Four names do not represent four equivalent evidence objects

Yohimbine hydrochloride and clenbuterol hydrochloride are small molecules with human pharmacology, but product identity and legal status vary by jurisdiction and source. Retatrutide is a defined investigational peptide studied in sponsor-controlled clinical development. 5-Amino-1MQ is a charged quinolinium small molecule used in preclinical research. It is not a peptide. Any commercial material requires independent identity, purity, counterion, concentration, impurity, and stability verification before biological interpretation.

Agent	Working identity	Intended target class	Highest directly relevant evidence identified	Status through cutoff
Yohimbine hydrochloride	Salt of yohimbine, an indole alkaloid	Alpha-2-adrenergic receptor antagonism with broader exposure-dependent pharmacology	Small acute human pharmacology and small body-composition studies	Human drug history varies by jurisdiction; supplement identity is unreliable
Clenbuterol hydrochloride	Long-acting beta-2-adrenergic agonist	Beta-2-adrenergic receptor agonism	Small randomized human acute, 2-week, and 4-week studies plus toxicity reports	No FDA-approved human drug in the United States; prohibited in sport
Retatrutide, LY3437943	Acylated single peptide agonist	GIPR, GLP-1R, and GCGR agonism	Randomized phase 1, phase 2, and phase 3 human trials	Investigational; not approved by any regulatory agency
5-Amino-1MQ	5-amino-1-methylquinolinium, commonly studied as a salt	NNMT inhibition	Cell and mouse pharmacology	Preclinical; no published human PK, safety, or efficacy study identified

3.2 Regulatory status is not a mechanistic endpoint

Regulatory status neither proves nor disproves a molecular mechanism. It does define what can be accurately said about human availability, quality, and established safety. FDA states that retatrutide is not a component of an approved drug, cannot be used in compounding under federal law, and has not been found safe and effective for any condition [27]. Lilly likewise describes retatrutide as investigational and available only in clinical trials [26].

Clenbuterol has been studied in humans and is used medically in some countries, but it is not an FDA-approved human drug in the United States. Poison-control and case literature document tachycardia, hypokalemia, myocardial injury, and other toxic effects [14,15]. WADA prohibits beta-2 agonists except narrow named inhaled exceptions; clenbuterol is not one of those exceptions [39].

For yohimbine, the distinction between pharmaceutical yohimbine hydrochloride and yohimbe supplements is critical. NCCIH reports wide variation and inaccurate labeling in supplement products, insufficient evidence for obesity, and cardiovascular and neurologic safety concerns [40]. A product label cannot substitute for an assay of the actual material.

3.3 Evidence asymmetry is the central systems property

The four-agent concept is not a balanced system in which four comparably understood nodes are being integrated. Retatrutide has multiweek randomized human outcome data. Yohimbine has a small set of older and heterogeneous human studies. Clenbuterol has small human studies that show context-dependent and sometimes unfavorable longer-duration findings. 5-Amino-1MQ has no identified human pharmacology. Any overall conclusion is therefore constrained by the weakest evidence layer, not strengthened by the number of proposed pathways.

4. Why acute lipolysis is not fat loss

Lipolysis is the hydrolysis of stored triacylglycerol into fatty acids and glycerol. A rise in circulating glycerol or non-esterified fatty acids can indicate increased mobilization, but it does not reveal how much fatty acid is oxidized, re-esterified, exported, or returned to storage. Human tracer work shows substantial fatty-acid cycling and re-esterification even when lipolytic flux is elevated [2,3].

The adipose lipid pool can be represented as:

EQUATION 1. ADIPOSE LIPID-POOL BALANCE

$$dF(t)/dt = L(t) + I(t) - O(t) - R(t) - X(t)$$

F(t) is stored adipose lipid. L(t) is lipid entering the modeled pool through local synthesis or modeled recirculation, depending on the declared compartment. I(t) is incoming lipid. O(t) is irreversible oxidation attributed to the relevant source. R(t) is re-esterification or return to storage. X(t) is net export from the modeled pool. Every term requires a declared compartment and measurement model. A transient increase in mobilization cannot determine dF(t)/dt by itself.

Whole-body stored energy follows the accounting identity:

EQUATION 2. DYNAMIC ENERGY BALANCE

$$dS(t)/dt = E_{in}(t) - E_{out}(t)$$

Here, S(t) is whole-body stored energy, $E_{in}(t)$ is energy intake, and $E_{out}(t)$ is energy expenditure. This identity is necessary but not a static "calorie deficit" predictor. Energy intake, expenditure, substrate

partitioning, glycogen, water, lean tissue, fat tissue, and adaptive responses change over time. Validated dynamic models explicitly account for these adaptations [1]. An acute percentage change in energy expenditure cannot be multiplied by weeks to produce a defensible fat-loss forecast.

5. Agent-level evidence

5.1 Yohimbine

5.1.1 Mechanistic proposition

Observed: Yohimbine antagonizes alpha-2-adrenergic receptors and can reduce alpha-2-mediated inhibition of lipolysis in human adipocytes. In a 1988 study, oral yohimbine increased plasma glycerol and non-esterified fatty acids in fasting healthy men. The response was enhanced during exercise, suppressed after a meal, and partly blocked by propranolol [4].

Inferred: The result is consistent with both peripheral alpha-2 blockade and increased norepinephrine availability. It does not isolate a single tissue or prove net fat loss.

Unknown: A reliable regional effect on lower abdominal, hip, or thigh fat is not established by that study. Depot differences in adrenergic receptor biology do not demonstrate controllable regional body-fat reduction in humans.

5.1.2 Pharmacokinetic variability

Yohimbine is absorbed and cleared rapidly in some individuals, but exposure varies widely. An older bioavailability study reported oral bioavailability ranging from 7 to 87 percent [5,6]. Yohimbine is metabolized to 10-hydroxy-yohimbine and 11-hydroxy-yohimbine, which retain alpha-2-antagonist activity [7]. A phase 1 study found yohimbine clearance to be strongly dependent on CYP2D6 genotype and reduced more than fivefold by paroxetine in extensive metabolizers [8].

The parent compound's short half-life therefore does not define a universal biological window. Active metabolites, genotype, inhibitor exposure, product identity, absorption, and fed state can all change the concentration-time profile.

5.1.3 Human outcome evidence

A randomized 21-day study in 20 male soccer players reported lower estimated fat mass with yohimbine than placebo, but no change in body mass, muscle mass, or performance [10]. The small sample, short duration, selected population, and body-composition method limit generalization. An older crossover study in women with obesity reported greater weight loss during a low-energy diet but did not find a significant lipolysis effect under its test conditions [41]. These studies do not establish a robust effect size, regional selectivity, or predictable response in a general population.

5.1.4 Safety

In a California Poison Control System review, common reported adverse events in yohimbine-containing product exposures included gastrointestinal distress, tachycardia, anxiety or agitation, and hypertension. Severe outcomes and healthcare-facility management were more frequent than for average poison-center exposures [9]. Most cases involved supplement products, which adds material-identity uncertainty rather than removing the safety signal.

5.1.5 Defensible conclusion

Yohimbine has bounded evidence for acute adrenergic and lipolytic effects in selected human conditions. It does not have strong evidence for reliable, regional, or sustained fat-mass reduction. Its exposure variability and sympathetic adverse-event profile are central to any interaction analysis.

5.2 Clenbuterol

5.2.1 Acute human pharmacology

Observed: In six healthy young men, a single clenbuterol exposure increased resting energy expenditure by 21 percent and fat oxidation by 39 percent during a 140-minute observation period. It also increased circulating glucose, lactate, insulin, and free fatty acids and increased skeletal-muscle mTOR phosphorylation [11].

Required boundary: This was an acute study with six participants. It does not show sustained energy expenditure, sustained fat oxidation, fat-mass reduction, or long-term safety. Phosphorylation is not equivalent to muscle hypertrophy or preservation.

5.2.2 Two-week human evidence

In a randomized crossover study of 11 healthy men, two weeks of clenbuterol increased lean mass by 0.91 kg but did not reduce fat mass. Maximal oxygen uptake fell by 7 percent and exercise capacity by 4 percent. Skeletal-muscle oxidative markers were reduced, and beta-2-adrenergic and ribosomal S6 signaling attenuated during repeated exposure [12].

This result directly contradicts a simple "continuous thermogenic drive" model. It also shows why a favorable body-composition component cannot be reported without performance and mechanistic costs.

5.2.3 Four-week human evidence

In a 2026 randomized crossover study of 14 adults with overweight or obesity, four weeks of clenbuterol did not significantly alter body weight, fat mass, fat-free mass, nocturnal energy expenditure, or nocturnal fat oxidation. Heart rate increased by about five beats per minute. The study found a modest increase in insulin-stimulated glucose uptake in one muscle region and a trend in another, but no improvement in whole-body or adipose-tissue insulin sensitivity [13].

This study is small and short, yet it is more relevant to sustained body-composition claims than an acute 140-minute study. It does not support the source manuscript's assertion of continuous daily lipolysis or dependable fat-mass reduction.

5.2.4 Safety and misuse evidence

Poison-control and case reports describe tachycardia, widened pulse pressure, hypokalemia, hyperglycemia, electrocardiographic changes, elevated troponin, chest pain, tremor, myocardial ischemia, and effects lasting more than 24 hours [14,15]. Case evidence cannot estimate incidence at a controlled exposure, but it establishes credible hazard modes that must be treated as guardrails.

5.2.5 Defensible conclusion

Clenbuterol can produce acute metabolic and signaling changes and short-term lean-mass gain in small studies. Longer-duration human evidence does not establish fat-mass reduction and identifies cardiovascular, cardiorespiratory, oxidative, and tolerance costs. The literature does not justify cycling instructions or a claim of sustained thermogenic benefit.

5.3 Retatrutide

5.3.1 Molecular design and early development

Retatrutide is a single acylated peptide agonist at the glucose-dependent insulinotropic polypeptide receptor, glucagon-like peptide-1 receptor, and glucagon receptor. Discovery studies combined in vitro pharmacology, obese-mouse experiments, and first-in-human data [16]. A 12-week phase 1b randomized trial in people with type 2 diabetes characterized multiple ascending exposures, pharmacokinetics, tolerability, glycemic effects, and body-weight change [17].

The engineered balance among three receptor activities is a property of the molecule under studied assay conditions. It does not mean that each receptor contributes a fixed percentage of clinical weight loss in a person.

5.3.2 Phase 2 obesity evidence

In a phase 2 double-blind randomized placebo-controlled trial of 338 adults with obesity or overweight plus a weight-related condition, mean body-weight change at 48 weeks ranged from -8.7 percent in the 1 mg group to -24.2 percent in the 12 mg group, compared with -2.1 percent with placebo [19]. Gastrointestinal adverse events were the most common. Dose-dependent heart-rate increases peaked at 24 weeks and declined thereafter.

This is strong evidence of treatment-associated body-weight reduction in the studied population. It is not evidence for the four-agent combination, and it does not erase the heart-rate or tolerability signal.

5.3.3 Type 2 diabetes and body composition

A phase 2 randomized trial in people with type 2 diabetes reported greater glycemic and body-weight improvements at several retatrutide exposures than placebo and dulaglutide [20]. A DXA substudy published in 2025 reported substantial total fat-mass reduction at higher studied exposures. Lean mass also decreased, and the proportion of lean-mass loss to total weight loss was similar to that seen with other obesity treatments [22].

The appropriate statement is that fat mass decreased more than lean mass in the studied subgroup. "Lean-mass sparing" or lean-mass gain is not established.

5.3.4 Liver fat and metabolic biomarkers

A phase 2a substudy using MRI-derived liver-fat measurements reported marked liver-fat reduction in participants with metabolic dysfunction-associated steatotic liver disease [21]. The study was not a biopsy-based histology trial and should not be generalized to fibrosis resolution or clinical liver outcomes.

An exploratory 2026 metabolomics and lipidomics analysis found changes in ketone and acylcarnitine clusters and other metabolic markers. Mediation models attributed only a minority of the weight response to the measured fatty-acid-oxidation cluster [23]. These data are compatible with altered substrate metabolism but do not prove that direct glucagon-receptor action explains the full clinical effect.

5.3.5 Gastric emptying and oral co-exposure uncertainty

Retatrutide delayed gastric emptying in a phase 1b substudy [18]. The direction and clinical size of an interaction with an oral co-administered agent cannot be inferred without measuring that agent's concentration-time profile. A delayed peak, lower peak, unchanged total exposure, or more variable exposure are different possibilities. The source manuscript converted this uncertainty into timing advice without supporting pharmacokinetic-interaction data.

5.3.6 Current phase 3 and regulatory state

A peer-reviewed 2026 phase 3 trial in 537 people with type 2 diabetes reported substantial glycemic and weight reductions at 40 weeks [24]. Sponsor topline releases from the TRIUMPH obesity program reported additional results in 2026, but complete peer-reviewed obesity phase 3 reports were not available through the evidence cutoff [25,26,42,43]. These disclosures must remain separate from peer-reviewed evidence.

Retatrutide remained investigational and not approved by any regulatory agency [26,27].

5.3.7 Defensible conclusion

Retatrutide has the strongest human outcome evidence among the four agents. Its clinical effects cannot be reduced to a single glucagon-mediated fat-oxidation pathway, and its gastrointestinal and heart-rate

effects are relevant to combination risk. Its efficacy as a single investigational agent does not validate a multi-agent stack.

5.4 5-Amino-1MQ

5.4.1 Target biology is not compound pharmacology

NNMT catalyzes methyl transfer from S-adenosylmethionine to nicotinamide, forming 1-methylnicotinamide and S-adenosylhomocysteine. In obese mice, antisense knockdown of Nnmt in adipose tissue and liver altered NAD+, S-adenosylmethionine, polyamine flux, oxygen consumption, and weight gain [28].

That study supports NNMT as a metabolic target in mice. It does not establish the human pharmacology of 5-Amino-1MQ.

5.4.2 Compound-specific cell and mouse evidence

The foundational compound paper characterized 5-Amino-1MQ and related quinolinium inhibitors in permeability, enzyme-selectivity, adipocyte, and diet-induced-obesity mouse experiments. 5-Amino-1MQ inhibited NNMT at low micromolar concentrations, reduced intracellular 1-methylnicotinamide, increased NAD+ and S-adenosylmethionine in adipocytes, and reduced weight and white-adipose measures in mice [29].

The compound's cell permeability and mouse efficacy are meaningful preclinical observations. They do not define oral human bioavailability, a human dose, long-term safety, or a human body-composition effect.

A 2021 mouse study combined NNMT inhibition with a reduced-calorie diet and reported additional body-composition and metabolic effects [32]. A related 2022 mouse study reported a distinct gut-microbiome pattern under the combined diet and NNMT-inhibition condition [33]. A 2024 study administered 5-Amino-1MQ to diet-induced-obese mice for 28 days, reported dose-dependent limitation of body-weight and fat-mass gain, improved metabolic measures, attenuated hepatic steatosis, and characterized mouse plasma pharmacokinetics and tissue distribution [34]. All remain animal studies.

5.4.3 Muscle-regeneration evidence

In aged mice with chemically injured tibialis anterior muscle, an NNMT inhibitor increased muscle stem-cell activity, myofiber cross-sectional area, and contractile recovery. Related cell experiments used C2C12 myoblasts [30]. This is an injury-regeneration model in aged mice. It does not establish lean-mass preservation during weight loss, anabolic efficacy in uninjured humans, or compatibility with the other agents.

5.4.4 Counterevidence and biological complexity

Genetic Nnmt deficiency produced sex- and diet-specific phenotypes in mice. It improved insulin sensitivity in some conditions but did not improve glucose tolerance consistently [31]. Target perturbation therefore does not produce a universal, monotonic metabolic benefit across models.

NNMT also participates in methyl-donor, nicotinamide, redox, and tissue-specific biology. Increasing NAD+ or altering S-adenosylmethionine cannot be assumed to be uniformly beneficial, and the magnitude and persistence of these changes in humans are unknown.

5.4.5 Human evidence gap

No published human pharmacokinetic, target-engagement, safety, efficacy, or interaction study of 5-Amino-1MQ was identified through 30 July 2026. The source manuscript's human timing, continuous-effect, fat-loss, lean-mass-preservation, and recovery projections are therefore unsupported.

5.4.6 Defensible conclusion

5-Amino-1MQ is a preclinical NNMT inhibitor with compound-specific cell and mouse evidence. It contributes the largest translational uncertainty to the four-agent hypothesis. Its addition cannot be treated as a known increase in oxidative capacity or as a human safety-neutral component.

6. Cross-agent evidence comparison

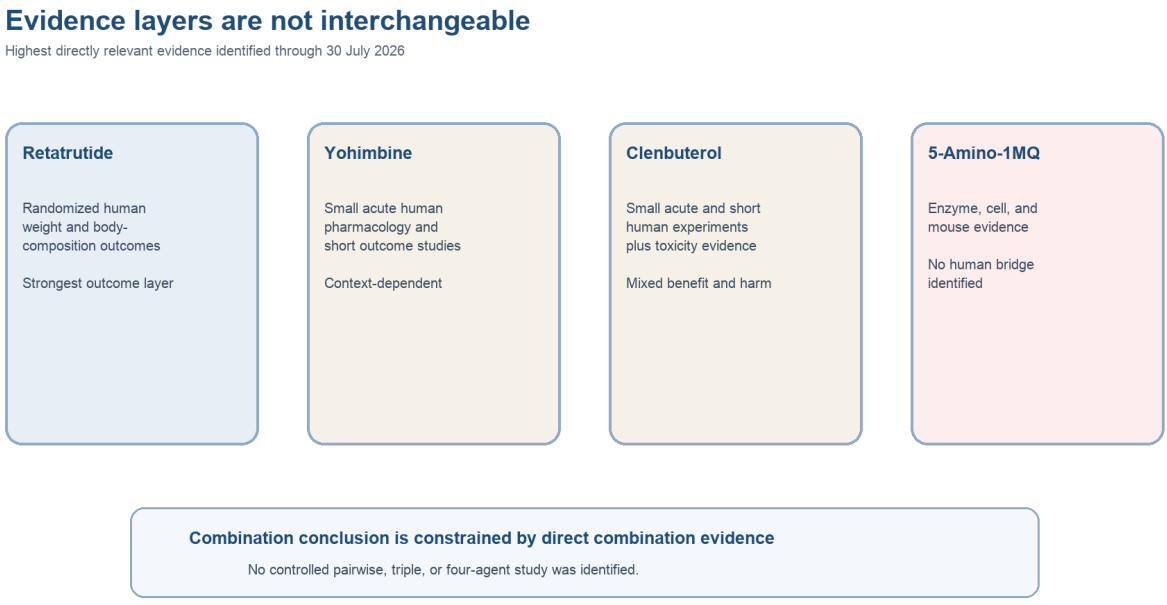


Figure 1. Evidence-layer asymmetry. The categories identify the highest directly relevant evidence located for each agent, not an efficacy ranking.

The four agents do not enter the hypothesis with equivalent evidence, regulatory status, target certainty, or time scale. Treating them as interchangeable "fat-loss pathways" obscures the central problem.

Agent	Direct human outcome evidence	Mechanistic evidence	Current interpretive status	Principal uncertainty
Yohimbine	Small, older, short studies with inconsistent body-composition and lipolysis findings	Human adrenergic and acute lipolysis studies	Limited human evidence for context-dependent acute effects; body-composition benefit not established	Product variability, CYP2D6-dependent exposure, cardiovascular and neuropsychiatric adverse effects
Clenbuterol	Small acute and short-duration human experiments; recent controlled studies do not establish fat-mass loss	Human beta-2-adrenergic, metabolic, muscle-signaling, and cardiorespiratory observations	Acute metabolic activity with tolerance and adverse-effect signals; sustained fat-loss claim unsupported	Cardiovascular toxicity, electrolyte disturbance, reduced aerobic capacity, regulatory and product-status concerns
Retatrutide	Randomized phase 1, phase 2, and phase 3 trials with substantial weight and fat-mass effects	Human receptor pharmacology, gastric-emptying, biomarker, body-composition, glycemic, and liver-fat studies	Strong single-agent human efficacy evidence; investigational at the evidence cutoff	Long-term outcomes, final regulatory evaluation, co-exposure pharmacokinetics, gastrointestinal and heart-rate effects
5-Amino-1MQ	None identified	Enzyme, cell, mouse obesity, mouse distribution, and mouse injury-regeneration studies	Preclinical only	Human identity, pharmacokinetics, target engagement, dose-response, safety, efficacy, and interaction profile

This asymmetry prevents any valid averaging of "mechanistic contribution." The retatrutide program supplies human outcome evidence. The yohimbine and clenbuterol literatures supply limited and partly discordant human observations. The 5-Amino-1MQ literature supplies a preclinical hypothesis. A four-agent conclusion cannot be stronger than the evidence for the combination itself, which was not identified.

7. Mechanistic complementarity, redundancy, and failure modes

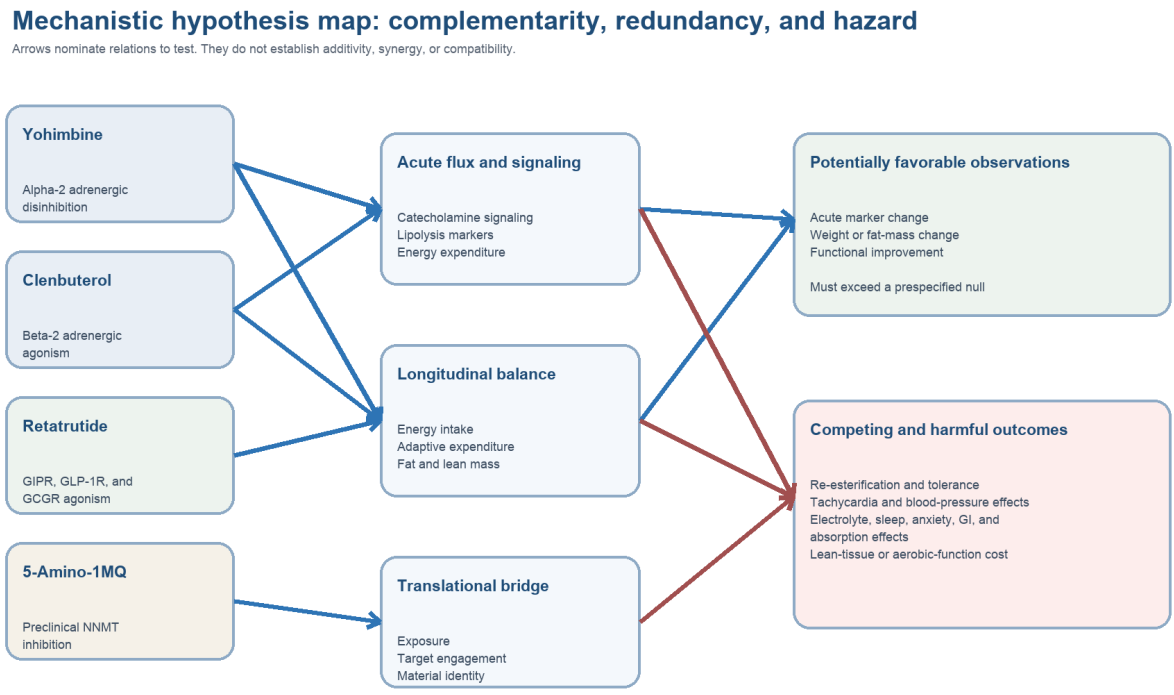


Figure 2. Mechanistic hypothesis map. Proposed pathways can converge on acute signals, longitudinal balance, or shared hazards. Every arrow is a relation to test.

7.1 A layered map of the proposed biology

The source manuscript linked four different control layers:

1. Yohimbine was assigned to presynaptic alpha-2-adrenergic disinhibition and context-dependent catecholamine-driven lipolysis.
2. Clenbuterol was assigned to beta-2-adrenergic signaling, acute thermogenesis, and muscle-related signaling.
3. Retatrutide was assigned to reduced energy intake, altered gastric emptying, glycemic regulation, and combined GIP, GLP-1, and glucagon receptor activity.
4. 5-Amino-1MQ was assigned to NNMT inhibition and intracellular nicotinamide and methyl-donor biology.

These assignments describe mechanistic domains. They do not demonstrate that the domains add, multiply, or remain independent when combined.

7.2 The strongest theoretical convergence

The most direct theoretical convergence is between yohimbine and clenbuterol. Alpha-2-receptor blockade can remove an inhibitory adrenergic signal, while beta-2-receptor agonism can stimulate cyclic-AMP-linked signaling. In a responsive adipose system, both could increase acute markers such as glycerol or non-esterified fatty acids.

That convergence supports a testable hypothesis of greater acute adrenergic perturbation. It does not establish greater net fat loss. The same convergence can also increase pulse, blood pressure, tremor, anxiety, arrhythmia risk, and metabolic disturbance. Mechanistic convergence can therefore amplify hazard without producing a favorable body-composition interaction.

Retatrutide acts on a longer clinical time scale and has a demonstrated single-agent effect on energy intake and body weight. Combining an effective intake-modifying agent with acute adrenergic stimulation is mechanistic complementarity in the ordinary-language sense. It is not statistical or pharmacological synergy.

The proposed role of 5-Amino-1MQ is more remote. Cell and mouse studies suggest that NNMT inhibition can alter cofactor pools and energy metabolism, but no human exposure-response bridge exists. The direction, magnitude, persistence, and tissue distribution of this effect in humans are unknown. It cannot be entered into a human combination model as a known positive term.

7.3 Pairwise adjudication

Pair	Plausible complementarity	Major competing explanation	Evidence status
Yohimbine plus clenbuterol	Greater acute adrenergic signaling and lipolysis markers	Redundant signaling, receptor desensitization, re-esterification, and disproportionate cardiovascular hazard	No controlled pairwise outcome study identified
Yohimbine plus retatrutide	Acute adrenergic perturbation alongside a longer-term reduction in energy intake	Yohimbine exposure variability, retatrutide-related gastric delay, and shared heart-rate burden	No controlled pairwise pharmacokinetic, safety, or efficacy study identified
Clenbuterol plus retatrutide	Acute beta-2 signaling alongside a longer-term energy-intake effect	Additive tachycardia, tolerance, impaired aerobic function, and no proof of added fat loss	No controlled pairwise outcome study identified
5-Amino-1MQ plus any agent	Theoretical intracellular cofactor modulation alongside extracellular receptor signaling	No human pharmacokinetic, target-engagement, safety, or efficacy bridge	No human pairwise study identified

7.4 Why apparently complementary pathways may fail

At least eight failure modes separate pathway diagrams from a favorable outcome:

1. **Rate limitation can move.** Increasing lipolysis does not ensure that liberated fatty acids are oxidized rather than re-esterified.
2. **Receptor tolerance can reduce persistence.** Repeated beta-2 stimulation can produce signaling adaptation, as seen in the short controlled clenbuterol literature [12,13].

3. **Endocrine context can reverse an acute signal.** Feeding and insulin can suppress the yohimbine-associated lipolysis response observed during fasting [4].
4. **Exposure can be unpredictable.** Yohimbine clearance varies with CYP2D6 activity and inhibition [8].
5. **Gastric delay can alter oral co-exposure.** Retatrutide can change gastric emptying, but the direction of any effect on an oral partner's concentration-time curve requires direct measurement [18].
6. **Adverse effects can constrain exposure.** Heart-rate, blood-pressure, electrolyte, sleep, gastrointestinal, and neuropsychiatric effects may become limiting before a favorable metabolic interaction is reached.
7. **Lean-tissue signals can be misread.** Short-term scale or DXA changes do not prove durable functional muscle gain, and retatrutide trials document some lean-mass loss during large total-weight reduction [22].
8. **Product identity can fail.** Unapproved or investigational materials acquired outside controlled supply chains may not match the material described in a publication.

7.5 Directional predictions that can be tested

The evidence supports only bounded, falsifiable predictions:

Observation	Bounded prediction	Confidence
Acute glycerol or non-esterified fatty acids	May rise with adrenergic perturbation under a permissive metabolic context	Moderate for single-agent yohimbine; low for the pair
Resting energy expenditure	May rise transiently after beta-2 stimulation	Moderate for an acute clenbuterol exposure; low for persistence
Body weight over months	Would most plausibly be dominated by retatrutide's established single-agent effect	Moderate, but no combination estimate is available
Fat mass	May decrease with retatrutide; an incremental contribution from the other agents is not estimable	Moderate for retatrutide alone; very low for the combination
Lean mass	Cannot be predicted as preserved or increased	Low
Heart rate and adrenergic symptoms	May be greater when agents with chronotropic or sympathomimetic effects overlap	Moderate mechanistic concern; combination incidence unknown
Human NNMT target engagement	Cannot be predicted from the available 5-Amino-1MQ literature	Very low

These are research hypotheses, not expected personal outcomes.

8. Time scale and exposure framework

8.1 Time scales must not be collapsed

The proposed mechanisms operate on different clocks:

Time scale	Relevant observations	Main interpretive limit
Minutes to hours	Adrenergic signaling, heart rate, blood pressure, glycerol, non-esterified fatty acids, resting energy expenditure, gastric emptying	Acute markers do not establish durable fat loss
Days to weeks	Receptor adaptation, sleep disruption, electrolyte effects, appetite changes, early weight change, exercise capacity	Water, glycogen, and lean-tissue changes can confound scale weight
Weeks to months	Fat mass, lean mass, waist circumference, glycemic control, liver fat, tolerability and discontinuation	Longer-term outcomes can be dominated by one agent and by adherence
Unknown in humans	5-Amino-1MQ pharmacokinetics, target engagement, tissue distribution, safety, and efficacy	No human bridge exists

The mismatch is important. A transient adrenergic spike cannot be added numerically to a 48- or 80-week weight-loss percentage. Likewise, a mouse exposure cannot be placed on the same time axis as a human clinical outcome without a pharmacokinetic and pharmacodynamic bridge.

8.2 A descriptive exposure model

For agent i, a minimal one-compartment description is:

EQUATION 3. MATHEMATICAL DEFINITION

$$dC_i(t)/dt = u_i(t)/V_i - k_{e,i}\, C_i(t)$$

Here, $C_i(t)$ is concentration, $u_i(t)$ is the input rate, V_i is an apparent distribution volume, and $k_{e,i}$ is an elimination-rate constant. This equation is not a dosing instruction. It shows why a clock time is not a mechanism: exposure depends on absorption, distribution, clearance, formulation, route, and repeated-input history.

For yohimbine, clearance variability is documented [8]. For retatrutide, slow peptide exposure and gastric effects create a different profile [17,18]. For clenbuterol, persistence and toxicodynamic effects can outlast the desired acute observation [14,15]. For 5-Amino-1MQ, the human terms are not known. No defensible four-agent exposure-overlap curve can therefore be calculated.

8.3 What a longitudinal study would need to observe

A valid study would separate:

1. concentration-time data for each material and relevant metabolites;
2. acute mechanistic markers;
3. cumulative energy intake and expenditure;

4. repeated body-composition measurements with a prespecified method;
5. functional outcomes rather than scale weight alone;
6. cardiovascular, neuropsychiatric, gastrointestinal, electrolyte, and hepatic safety;
7. adherence, product identity, and discontinuation;
8. delayed or persistent adverse effects.

Without these measurements, a period-of-time narrative remains an unquantified scenario.

9. Quantitative interaction framework

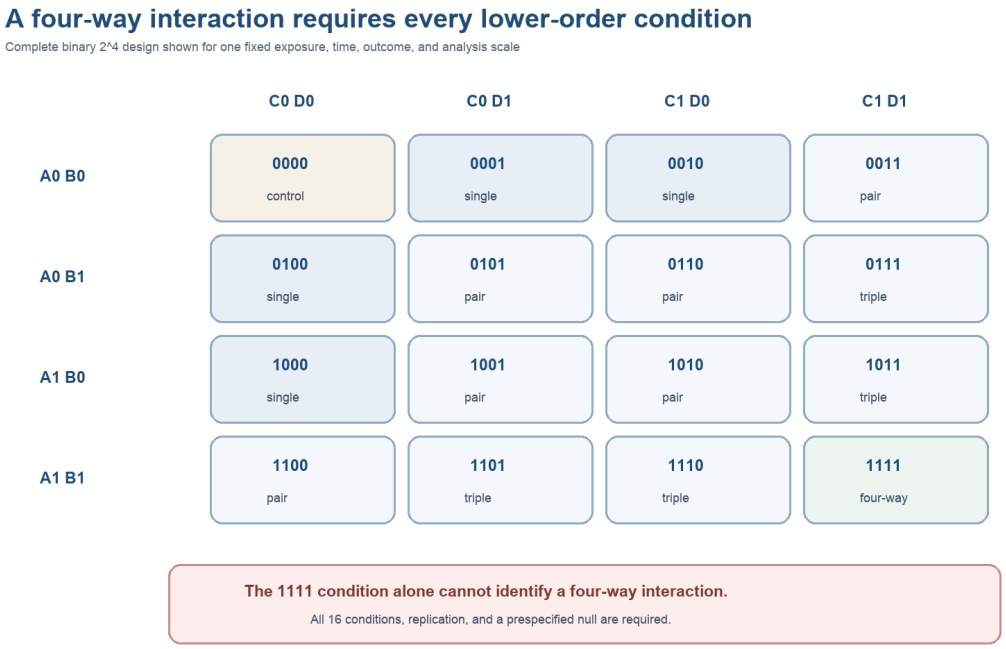


Figure 3. Complete binary four-factor design. The four-agent condition cannot identify interaction without the control, singles, pairs, and triples.

9.1 The estimand must be named before the model

Let Y denote one prespecified outcome at one prespecified time and analysis scale. Examples include change in fat mass, change in resting energy expenditure, or a cardiovascular safety endpoint. The same combination can be favorable for one outcome and harmful for another. "Overall synergy" is therefore not a single observable quantity.

For a pair of binary inputs i and j, define:

EQUATION 4. MATHEMATICAL DEFINITION

$$\Delta_{ij}(t) = \mu_{11}(t) - \mu_{10}(t) - \mu_{01}(t) + \mu_{00}(t)$$

where $\mu_{a\beta}(t)$ is the mean outcome at time t when input i=a and input j=b. Equation 4 is an additive-scale interaction contrast. It is not invariant to outcome transformation, and it is not a universal coefficient of biological synergy.

9.2 Four-way interaction

For four binary inputs A, B, C, and D, the pure four-way contrast is:

EQUATION 5. MATHEMATICAL DEFINITION

$$\Delta_4(t) = \Sigma_{s\subseteq\{A,B,C,D\}} (-1)^{4-|S|} \mu_s(t)$$

The contrast requires all 16 cells of a complete 2^4 factorial design, including the no-agent condition, four single-agent conditions, six pairs, four triples, and the four-agent condition. It cannot be inferred from four monotherapy literatures or from the fully combined condition alone.

Equation 5 also does not answer whether a result is clinically useful. A statistically nonzero contrast could be small, harmful, or driven by a scale artifact.

9.3 Dose, time, and response surfaces

Binary contrasts are inadequate when effects vary across concentration and time. A more general model is:

EQUATION 6. MATHEMATICAL DEFINITION

$$g\{E[Y(d,t)]\} = \alpha + \Sigma_i f_i(d_i,t) + \Sigma_{i<j} f_{ij}(d_i,d_j,t) + \text{higher-order terms}$$

The main effects must satisfy $f_i(0,t)=0$, and pairwise terms must satisfy $f_{ij}(d_i,0,t)=f_{ij}(0,d_j,t)=0$. Comparable constraints are required for higher-order terms. Without them, main and interaction functions are not separately identifiable.

Bliss independence, Loewe additivity, highest-single-agent comparison, and response-surface models answer different questions and make different assumptions [35-38]. A null model must be selected before examining the data. MuSyC can separate potency and efficacy interactions in suitable pairwise concentration-response data [36]. SynergyFinder implements several common reference models [37]. Neither can rescue a design that lacks measured combination cells, replication, exposure verification, or a suitable outcome.

9.4 Energy storage remains the clinical bridge

A minimal energy-storage identity is:

EQUATION 7. MATHEMATICAL DEFINITION

$$dS(t)/dt = E_{in}(t) - E_{out}(t)$$

The identity does not imply that intake and expenditure are fixed or independently controlled. Both can adapt with body size, diet composition, activity, endocrine state, symptoms, and treatment [1]. An acute change in lipolysis belongs inside this dynamic system. It is not an additional term that bypasses energy conservation.

9.5 Joint benefit and joint harm require separate models

A time-to-event safety model could be written as:

EQUATION 8. MATHEMATICAL DEFINITION

$$\lambda(t) = \lambda_0(t) \exp\{\Sigma_i \beta_i E_i(t) + \Sigma_{i<j} \beta_{ij} E_i(t)E_j(t)\}$$

Here, $E_i(t)$ is a verified exposure measure. The coefficients are unknown for the proposed combination. Equation 8 states the data requirement; it does not estimate risk.

A study should not collapse efficacy and safety into an unvalidated score. At minimum, it should report:

1. the prespecified efficacy estimand;
2. each safety endpoint and its uncertainty;
3. discontinuation and missing-data patterns;
4. single-agent, pairwise, and higher-order contrasts;
5. absolute effects, not only percent changes;
6. sensitivity to the null model and outcome scale;
7. multiplicity control and model diagnostics.

10. Interaction-risk analysis

10.1 Cardiovascular and autonomic convergence

Yohimbine and clenbuterol both perturb adrenergic physiology. Retatrutide trials also reported heart-rate increases [19]. The combination therefore creates a credible direction of shared chronotropic and autonomic burden even though its incidence and magnitude are unknown.

The absence of a documented four-agent adverse event is not reassurance. It primarily reflects the absence of a controlled four-agent study.

10.2 Gastrointestinal and oral-exposure uncertainty

Retatrutide can produce nausea, vomiting, diarrhea, constipation, and delayed gastric emptying [18-24]. Gastrointestinal effects can alter hydration, food intake, tolerability, and potentially the rate or variability of absorption of oral co-exposures. An oral interaction cannot be assumed to be solved by separating clock times. It requires measured concentration-time data.

10.3 Metabolic, electrolyte, and exercise risk

Beta-2 stimulation can shift potassium and glucose handling. Poison-control reports and clinical cases identify hypokalemia, hyperglycemia, tachycardia, electrocardiographic abnormalities, chest pain, and myocardial injury after clenbuterol exposure [14,15]. Short controlled data also indicate reduced maximal oxygen uptake and exercise capacity [12].

These observations directly oppose the source manuscript's assumption that a metabolic signal can be evaluated without cardiorespiratory cost.

10.4 Neuropsychiatric and sleep effects

Yohimbine-associated poison reports commonly include anxiety and agitation [9]. Clenbuterol can produce tremor and stimulant-like symptoms [14,15]. Sleep disruption, anxiety, or reduced exercise tolerance can undermine the behavioral and physiological conditions needed for sustained body-composition change.

10.5 Material and regulatory risk

Retatrutide was investigational through the cutoff, and the United States Food and Drug Administration stated that retatrutide cannot be used in compounding under federal law and has not been found safe or effective for any condition [27]. Clenbuterol is not an FDA-approved human drug in the United States and is prohibited in sport [14,39]. No authorized human 5-Amino-1MQ product or human clinical evidence was identified.

Product identity, concentration, sterility where applicable, impurity profile, counterion, storage history, and chain of custody are therefore not secondary details. A publication cannot transfer evidence from a characterized research material to an unverified commercial label.

10.6 Risk matrix

Risk domain	Yohimbine	Clenbuterol	Retatrutide	5-Amino-1MQ	Combination concern
Heart rate and blood pressure	Established concern	Established concern	Heart-rate signal in trials	Unknown	Plausible shared burden
Arrhythmia and myocardial injury	Reported adverse events	Reported toxicity	Not established as a combination effect	Unknown	No controlled incidence estimate
Anxiety, agitation, tremor, sleep	Established concern	Established concern	Secondary to tolerability in some individuals	Unknown	Functional and adherence burden may rise
Gastrointestinal effects and absorption	Variable oral exposure	Oral exposure may be affected	Established gastrointestinal and gastric-emptying effects	Human absorption unknown	Unmeasured pharmacokinetic interaction
Glucose and electrolyte handling	Adrenergic effects possible	Established concern	Glycemic effects are therapeutic but context-dependent	Unknown	Monitoring requirements cannot be inferred
Lean mass and function	Not established	Short-term lean signal with aerobic cost	Lean mass decreases with large weight loss	Mouse injury model only	Preservation or gain cannot be assumed
Material identity	Supplement variability	Unapproved human use in United States	Investigational	Research material only	Evidence transfer may fail at the material level

11. Validation pathway

11.1 Stage 0: material identity and source custody

Before any mechanistic interpretation, each material requires:

1. unambiguous chemical or biological identity;
2. sequence or structure, stereochemistry, terminal chemistry, salt or counterion, and formulation where relevant;
3. lot-specific purity, impurity, potency, and stability data;
4. validated analytical methods and chain of custody;
5. source-document hashes and provenance;
6. a distinction between the administered material, the active species, and the measured biological perturbation.

Failure at this stage invalidates evidence transfer.

11.2 Stage 1: single-agent translational gaps

The largest prerequisite is not a four-agent trial. It is a defensible human bridge for 5-Amino-1MQ, including pharmacokinetics, target engagement, dose-response, safety, metabolism, and tissue exposure. Product-independent yohimbine exposure verification and clinically relevant clenbuterol safety constraints would also be required.

An investigational retatrutide study would require sponsor, regulatory, and ethics authorization. Clenbuterol's regulatory status and known toxicity may make a human body-composition combination study ethically unacceptable. A theoretical design does not confer ethical feasibility.

11.3 Stage 2: mechanistic pairwise testing

Validated model systems should test the most credible pairwise hypotheses before any higher-order combination:

1. yohimbine plus a beta-2 perturbation for acute adrenergic signaling, lipolysis, re-esterification, and cytotoxic or stress responses;
2. retatrutide-related gastric effects plus oral-agent pharmacokinetics in a suitable model;
3. NNMT inhibition plus extracellular receptor perturbations with measured target engagement;
4. safety-relevant cardiovascular, electrophysiologic, electrolyte, and metabolic endpoints.

Each study requires a prespecified noninteraction model, concentration matrix, time course, biological replication, batch control, and uncertainty intervals.

11.4 Stage 3: complete interaction design

If and only if the single-agent and pairwise gates are satisfied, a complete factorial or response-surface design is needed to estimate higher-order interaction. For fixed binary exposures, the complete design has 16 conditions. For continuous exposures, the number of conditions increases rapidly and should be selected using an explicit design-of-experiments strategy.

The design must not compare only the full combination with a control. That contrast cannot identify which agent contributed, whether a pair was redundant, or whether the four-way term differed from zero.

11.5 Stage 4: longitudinal outcomes

A clinically meaningful program would need separate primary and safety objectives. Candidate efficacy outcomes include validated fat mass, total body weight, waist circumference, energy intake, and functional measures. Mechanistic endpoints can include concentrations, metabolites, target engagement, indirect calorimetry, substrate flux, and appropriate signaling markers. Safety endpoints require continuous or repeated cardiovascular assessment, laboratory testing, adverse-event adjudication, discontinuation rules, and long enough follow-up to identify persistence.

The statistical analysis plan should be public before unblinding. It should define estimands, missing-data handling, model assumptions, multiplicity, clinically meaningful thresholds, and stopping rules. Raw or appropriately de-identified data and executable analysis code should be preserved.

11.6 Required decision gates

Gate	Pass condition	Failure consequence
Identity	All materials and source records analytically reconciled	Stop; no biological interpretation
Single-agent bridge	Exposure, target engagement, and safety are characterized in the relevant system	Stop; no combination inference
Pairwise mechanism	Replicated interaction relative to a prespecified null with measured exposure	Do not advance the pair
Safety	No failed cardiovascular, metabolic, neuropsychiatric, gastrointestinal, or material guardrail	Stop regardless of efficacy signal
Higher-order design	All required cells, replication, and model constraints are present	Do not use "synergy"
Longitudinal relevance	Acute markers predict a prespecified durable outcome	Restrict claims to acute mechanism
Reproducibility	Independent replication or external validation	Label as provisional

12. Adjudication of the source manuscript's major claims

Source claim or implication	Adjudication	Defensible replacement
The four agents form a synergistic system	Unsupported	They form a testable multi-layer hypothesis with no controlled combination evidence
Yohimbine preferentially removes resistant regional fat	Not established as a durable human body-composition effect	Human acute lipolysis is context-dependent; regional fat-loss benefit is unproven
Clenbuterol supplies sustained thermogenesis	Unsupported and challenged by adaptation data	Acute energy-expenditure effects exist, but persistence and fat-mass benefit are not established
Retatrutide provides direct fat oxidation that can be added to the adrenergic agents	Over-simplified	Retatrutide has strong single-agent weight-loss evidence through several physiological pathways; an incremental combination effect is unknown
5-Amino-1MQ increases human oxidative capacity and fat loss	Unsupported in humans	Cell and mouse studies support a preclinical NNMT-inhibition hypothesis
The combination preserves or increases lean mass	Unsupported	Retatrutide-related weight loss includes some lean-mass loss; short clenbuterol findings do not establish durable functional preservation
Clock timing creates mechanistic synergy	Unsupported	Exposure overlap and interaction require direct pharmacokinetic and pharmacodynamic measurement
Faster fat loss can be predicted	Unsupported	No combination effect size, variance, or time course can be estimated
The risk profile can be inferred from each agent separately	Unsafe inference	Shared adrenergic, chronotropic, gastrointestinal, absorption, electrolyte, and material risks require combination data

13. Discussion

13.1 What the evidence supports

The four-agent proposal contains biologically plausible pieces, but plausibility is uneven. Retatrutide has a substantial and expanding human clinical program. Yohimbine has evidence for context-dependent adrenergic and lipolytic effects plus limited short body-composition studies. Clenbuterol produces acute metabolic and muscle signals but also adaptation, impaired aerobic performance, and credible cardiovascular toxicity. 5-Amino-1MQ has compound-specific cell and mouse evidence without a human bridge.

The most defensible synthesis is therefore not a protocol and not a predicted stack outcome. It is an evidence map with a set of falsifiable interaction hypotheses and explicit stop conditions.

13.2 Which component would most plausibly dominate a longitudinal outcome

If substantial weight loss occurred during exposure to the four labels, the existing literature would make retatrutide the most plausible dominant contributor. That inference is based on replicated randomized human outcomes for retatrutide and the absence of comparable evidence for the other three agents. It would still require verified exposure and cannot assign an individual counterfactual effect.

The acute adrenergic agents might change short-term physiological markers without materially increasing long-term fat loss. 5-Amino-1MQ might contribute no measurable human effect, an unrecognized effect, or harm. The current evidence cannot choose among those possibilities.

13.3 Why more pathways do not guarantee a better system

Adding components can introduce redundancy, antagonism, pharmacokinetic interference, adaptive compensation, measurement noise, and shared toxicity. A pathway diagram counts arrows. A defensible system model measures states, exposures, interactions, uncertainty, and failure.

The relevant comparison is not "four mechanisms versus one mechanism." It is the full combination versus its best supported single agent and every required lower-order condition, on both benefit and harm endpoints.

13.4 Generalizability

The cited human studies differ in population, duration, formulation, metabolic state, training status, diet, outcome definition, and analytical method. Results from healthy men, trained athletes, people with obesity, people with type 2 diabetes, and poison-control cases are not directly exchangeable. Mouse NNMT inhibition and chemically injured muscle models are still further removed.

Any claim must remain bounded to the study material, system, exposure, and outcome.

14. Limitations of this paper

This is a critical, evidence-mapping analysis, not a registered systematic review or meta-analysis. Searches prioritized primary papers, trial registries, regulators, and sponsor disclosures known by 30 July 2026. A missed or newly published study could change an agent-specific conclusion.

Absence of an identified combination study is not proof that no private, unpublished, or unindexed experiment exists. It means no public evidence sufficient for a defensible claim was located.

Several literatures are small. Yohimbine and clenbuterol studies often involve few participants, short durations, older methods, or nonrepresentative populations. Poison-control and case reports establish hazards but do not estimate incidence under controlled conditions.

The retatrutide evidence base is changing rapidly. Sponsor topline phase 3 disclosures were included only as non-peer-reviewed status evidence and were not treated as substitutes for full reports [42,43].

No independent analytical testing of any commercial product was performed. This paper does not establish identity, purity, exposure, safety, efficacy, or suitability of a material offered under any of the four labels.

The quantitative equations define estimands and data requirements. They are not fitted models because no complete combination dataset was identified.

15. Conclusions

The source manuscript's central error was to convert four heterogeneous literatures into an operational protocol and to label theoretical pathway complementarity as synergy.

The revised evidence supports five conclusions:

1. Retatrutide has strong single-agent human weight-loss evidence but remained investigational at the cutoff.
2. Yohimbine can alter acute adrenergic and lipolysis measures in a context-dependent manner, but durable body-composition benefit is not established.
3. Clenbuterol can alter acute metabolism and muscle signaling, but sustained fat-mass benefit is not established and cardiovascular, electrolyte, cardiorespiratory, and tolerance concerns are material.
4. 5-Amino-1MQ is a preclinical NNMT inhibitor without an identified human pharmacokinetic, safety, target-engagement, or efficacy study.
5. No pairwise, triple, or four-agent study was identified. No magnitude, timing, safety, efficacy, or synergy of the combination can be predicted.

The four-agent concept is suitable only as a staged research hypothesis. It requires verified materials, single-agent translational bridges, pairwise concentration-time experiments, a complete interaction design, longitudinal outcomes, and independent safety guardrails. Until those conditions are satisfied, no protocol, expected result, regional fat-loss claim, lean-mass-preservation claim, or clinical recommendation is defensible.

16. Claim register

ID	Bounded proposition	Evidence class	Confidence	Permitted wording
C01	Retatrutide reduced body weight in randomized human trials	Peer-reviewed randomized clinical trials	High for studied populations	"Reduced body weight under studied trial conditions"
C02	Retatrutide reduced total fat mass and also reduced lean mass in a DXA substudy	Peer-reviewed substudy	Moderate	"Fat mass decreased; lean mass also decreased"
C03	Retatrutide can delay gastric emptying	Peer-reviewed phase 1b substudy	Moderate	"Delayed gastric emptying under studied conditions"
C04	Retatrutide was investigational at the evidence cutoff	Regulator and sponsor status sources	High	"Investigational and not approved at the cutoff"
C05	Yohimbine can increase acute lipolysis under fasting adrenergic conditions	Small human mechanistic studies	Moderate	"Produced a context-dependent acute lipolysis signal"
C06	Yohimbine has established durable regional fat-loss efficacy	No adequate evidence	Very low	Not permitted
C07	Yohimbine exposure varies with metabolism and CYP2D6 inhibition	Human pharmacokinetic evidence	Moderate	"Exposure can vary substantially"
C08	Clenbuterol can acutely increase resting energy expenditure and fat oxidation	Small human acute study	Moderate	"Produced an acute effect in a small study"
C09	Clenbuterol produces sustained human fat-mass loss	Controlled data do not establish this	Very low	Not permitted

ID	Bounded proposition	Evidence class	Confidence	Permitted wording
C10	Clenbuterol can impair aerobic capacity and produces material cardiovascular and metabolic hazards	Human controlled and toxicology evidence	Moderate to high	"Carries material safety and functional concerns"
C11	NNMT is a metabolically relevant target in mouse models	Genetic and pharmacological mouse studies	Moderate for mice	"Supports a preclinical target hypothesis"
C12	5-Amino-1MQ inhibits NNMT and altered weight or adipose outcomes in mice	Compound-specific preclinical studies	Moderate for studied models	"Produced preclinical effects in cell and mouse studies"
C13	5-Amino-1MQ is effective or safe for human fat loss	No human study identified	Very low	Not permitted
C14	The four agents have complementary theoretical control layers	Mechanistic synthesis	Low to moderate	"Mechanistically complementary hypothesis"
C15	The four-agent combination is synergistic	No complete interaction experiment	Very low	Not permitted
C16	The combination will preserve lean mass or accelerate fat loss	No controlled combination outcome data	Very low	Not permitted
C17	The combination can increase shared cardiovascular or autonomic burden	Mechanistic convergence plus single-agent human safety data	Moderate concern	"Plausible shared hazard requiring direct study"

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