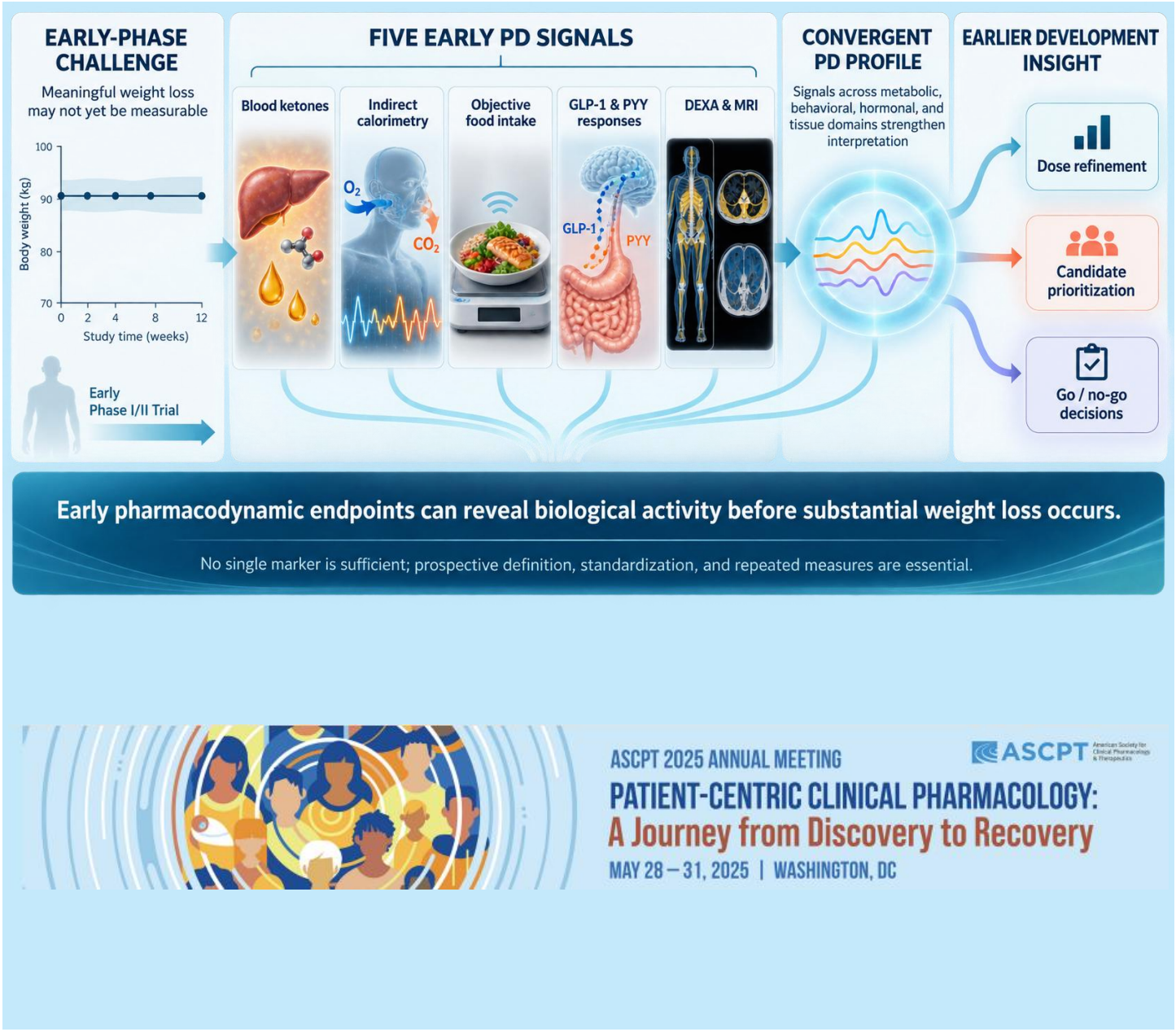
Pharmacodynamic Models for Predicting Weight Loss Efficacy in Early-Phase Trials

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Pharmacodynamic Models for Predicting Weight Loss Efficacy in Early-Phase Trials

Dehn C [1,3,4], Agarwal N [1,3,4,5], Atella-Targum M [1,4], Ballester L [2,3], Bianco J [1,4], Cassidy C [1,4], Chastain A [1,4], Eakin A [1,4,5], Fuquay A [1,4], Harley E [1,4], Hennessy D [1,4], Hunter S [1,4], Isaac Y [1,4,5], Karnes T [1,4], Konis G [1,4,5], Kramer L [1,4], Kulikova R [1,4,5], Kwan H [1,4,5], Maroney S [1,4], McPherson K [2,3], Minkowitz H [1,4], Patel P [1,4], Poole A [1,4], Popovitz M [1,4], Praul J [1,4], Prezioso A [1,4,5], Ridolfi E [1,4], Rosales J [1,4], Schwartz S [1,4], Solanki D [1,4,5], Springer J [1,4,5], Tireman E [2,3], Wright L [1,4], Martin W [2,3,4]

[1] **Evolution Research Group (ERG):** A network of clinical research sites conducting trials across all phases, with specialized expertise in early-phase and complex clinical research in neuroscience, endocrinology, and metabolic disorders. ERG supports clinical conduct, investigator engagement, and scientific leadership across a broad range of therapeutic areas.

[2] **Lotus CRO:** A full-service contract research organization that provides comprehensive clinical trial support, from protocol development through regulatory submission. Lotus works with both ERG-affiliated and independent research sites, with a dedicated focus on metabolism, endocrinology, and other complex therapeutic areas.

[3] **Lotus/ERG Publication & Dissemination Group:** A cross-functional working group dedicated to ensuring the quality, rigor, and integrity of scientific outputs across Lotus and ERG.

[4] **ERG Obesity Task Force:** A dynamic, multi-stakeholder initiative focused on the strategic execution of clinical trials in the obesity space.

[5] **ERG ABOM Investigator Team:** A cohort of physicians committed to advancing the standard of care through board certification in obesity medicine and leadership in clinical trial excellence.

ABSTRACT

Early-phase clinical trials for anti-obesity drugs are often too short to observe significant weight loss, necessitating surrogate markers of efficacy. This white paper identifies key pharmacodynamic (PD) biomarkers that can bridge this gap. A narrative review highlighted five PD methodologies: blood ketone levels, indirect calorimetry metrics, laboratory eating behavior monitoring, gut hormone responses, and body composition analyses. Each method taps into a physiological mechanism such as fat oxidation, energy expenditure, appetite regulation, hormonal satiety signals, or fat mass reduction that manifests before appreciable weight change.

Integrating these PD markers into Phase I/II trials could enable drug developers to gauge efficacy earlier. This approach may accelerate go/no-go decisions and reduce time to proof-of-concept. A structured implementation of early PD endpoints can demonstrate early onset of pharmacologic activity, offering timely evidence of efficacy that may support more informed development decisions and enable greater scientific and operational efficiency.

INTRODUCTION

Demonstrating weight-loss efficacy in Phase I/II trials is challenging because meaningful weight reduction typically requires extended treatment duration[1]. Early-stage studies primarily assess safety and pharmacokinetics, often lacking reliable signs of whether the intervention will ultimately induce weight loss. This delay in efficacy readouts can slow development and increase costs, as decisions to advance a compound may rely on late-phase outcomes.

Pharmacodynamic biomarkers offer a solution by serving as surrogate endpoints that reflect the drug's physiological impact before observable weight change. In drug development for chronic conditions, validated surrogate markers have significantly improved development efficiency[2]. For obesity therapeutics, early changes in metabolism, behavior, or hormones might predict long-term weight loss. By identifying PD signals of negative energy balance or appetite suppression, researchers can infer efficacy potential sooner.

This paper identifies PD models that may serve as early indicators of weight loss efficacy, presenting their mechanistic physiological underpinnings and summarizing evidence to support their predictive utility. Each technique is reviewed in terms of feasibility, mechanistic rationale, and alignment with clinical trial needs in early-phase development.

METHODS

This project was based on a narrative review of scientific literature, supplemented by domain expertise in metabolism, clinical pharmacology, and early-phase trial design. The aim was to identify pharmacodynamic (PD) measures that could serve as early efficacy indicators in weight loss interventions, particularly those observable within the limited duration of Phase I or Phase IIa trials.

A targeted search strategy was used to retrieve peer-reviewed articles, clinical trial reports, and mechanistic studies relevant to the biological effects of anti-obesity interventions. Searches were conducted using terms such as "early biomarker," "surrogate endpoint," "weight loss predictor," "ketone bodies," "indirect calorimetry," "appetite regulation," "GLP-1," "PYY," "DEXA," and "body composition." Methods were included if they demonstrated detectable pharmacodynamic effects within 6 weeks of treatment initiation and were mechanistically linked to or predictive of subsequent weight loss. This window was selected to reflect the time constraints typical of early-phase studies, while acknowledging that certain tools, such as the Universal Eating Monitor, may reveal treatment effects even after a single exposure. The focus was on human studies wherever possible, with preclinical data considered only when mechanistic insights were directly translatable. Data were grouped into five major PD model domains: circulating metabolic biomarkers, indirect calorimetry, objective food intake measurement, gut hormone responses, and body composition analysis. Although the review was not systematic, care was taken to ensure transparency in how sources were identified and selected.

The focus was on human studies wherever possible. Preclinical data were included only when mechanistic insights were directly translatable to clinical settings. Data were grouped into five major PD model domains:

- Circulating metabolic biomarkers (e.g., blood ketones),
- Indirect calorimetry (e.g., respiratory quotient and energy expenditure),
- Objective food intake measurement (e.g., Universal Eating Monitor),
- Gut hormone responses (e.g., GLP-1 and PYY), and
- Body composition analysis (e.g., DEXA, MRI).

This review synthesizes findings from representative studies within each domain to provide practical insights for drug developers considering these endpoints in early-phase clinical trials.

Pharmacodynamic Models as Early Predictors of Weight Loss Efficacy

Each of the following pharmacodynamic models is described in terms of (1) physiological mechanism, (2) rationale for use in early-phase clinical trials, and (3) supporting evidence. While these methods vary in complexity, invasiveness, and interpretive nuance, they share the potential to provide measurable, early indications of therapeutic efficacy before substantial reductions in body weight have occurred.

Circulating Metabolic Biomarkers: Blood Ketones (β-Hydroxybutyrate)

Physiological Mechanism:

β-Hydroxybutyrate (BHB) is one of three principal ketone bodies produced in the liver from fatty acids during periods of reduced carbohydrate availability or prolonged energy deficit. Elevated levels of BHB reflect a shift toward increased fat oxidation, decreased insulin levels, and hepatic ketogenesis. Ketogenesis is typically initiated after glycogen stores are depleted, suggesting that the body has moved into a negative energy balance and is mobilizing fat stores for energy.

Operational Notes:

Circulating levels of β-hydroxybutyrate (BHB) for these purposes are most commonly measured from blood samples. Depending on the study context, measurement can be performed through a local safety laboratory, a central bioanalytical laboratory, or point-of-care systems using fingerstick capillary blood. When used under standardized timing and fasting conditions, all of these approaches can provide interpretable data suitable for evaluating early shifts in substrate utilization. Selection of method should balance assay sensitivity, logistical feasibility, and the level of analytical precision required by the study design.

Rationale for Early Use:

Because circulating BHB levels can rise within 24 to 72 hours of initiating a calorie-restricted diet or metabolic intervention, they represent a timely and accessible biomarker of acute fat oxidation[3]. In early-phase trials where weight change is minimal or slow to emerge, elevations in BHB can serve as an early indicator of target engagement and expected downstream efficacy. BHB may be especially relevant in the context of therapies that induce carbohydrate restriction, modulate insulin sensitivity, or directly promote fatty acid mobilization and oxidation.

Supporting Evidence:

In a prospective analysis of adults with severe obesity undergoing a meal replacement intervention, Finucane et al. reported that weight loss was directly proportional to increases in fasting BHB concentrations[3]. Participants with the greatest early rise in BHB experienced the most substantial weight reduction at the end of the program. These findings support the concept that early ketogenesis is not only mechanistically expected but also quantitatively predictive of long-term response. Additional studies have shown that elevated BHB is associated with appetite suppression and increased satiety, potentially offering dual utility as both a metabolic and behavioral biomarker[4].

Indirect Calorimetry: Resting Energy Expenditure and Respiratory Quotient

Physiological Mechanism:

Indirect calorimetry is a noninvasive technique that quantifies whole-body energy expenditure and substrate utilization by measuring oxygen consumption (VO_2) and carbon dioxide production (VCO_2). Two key outputs from this method are resting energy expenditure (REE) and the respiratory quotient (RQ). REE reflects baseline caloric burn at rest, while RQ (calculated as VCO_2/VO_2) indicates the relative mix of substrates being oxidized. An RQ of ~0.7 suggests predominant fat oxidation, while values near 1.0 suggest carbohydrate oxidation.

Operational Notes:

Indirect calorimetry is typically performed using a full metabolic cart system in a thermoneutral, fasting state. These systems simultaneously measure oxygen consumption (VO_2) and carbon dioxide production

(VCO_2) to calculate respiratory quotient and resting energy expenditure. Modern portable indirect calorimeters have improved upon earlier handheld devices by enabling direct measurement of both VO_2 and VCO_2 with validated accuracy. These alternatives, when validated and used under standardized conditions, may offer operational flexibility while preserving measurement integrity in early-phase settings.

Rationale for Early Use:

Pharmacologic interventions that alter appetite, energy intake, or thermogenesis may produce early shifts in energy balance and substrate utilization. A decrease in RQ within the first days or weeks of treatment suggests increased fat oxidation, even before observable weight change occurs. When measured under standardized conditions (e.g., morning, fasting, thermoneutral environment), RQ offers a reproducible, physiologically grounded readout that reflects substrate utilization and can provide early insight into treatment engagement.

Resting energy expenditure (REE), in contrast, reflects the total energy expended at rest and is directionally responsive to interventions that influence thermogenesis or adaptive metabolic slowing. An increase in REE may indicate enhanced thermogenesis or a mitigation of energy-conserving adaptations, both of which are potentially favorable in the context of weight-loss interventions. However, interpretation of REE changes should be contextualized within the broader metabolic profile and mechanism of action of the therapy.

Supporting Evidence:

Lim et al. hypothesized and demonstrated that RQ could serve as an early indicator of negative energy balance in individuals undergoing weight loss[5]. Participants with greater early reductions in RQ, which indicate a metabolic shift from carbohydrate to fat oxidation, were more likely to exhibit greater long-term weight loss. Similar observations have been made in studies of caloric restriction, where decreases in RQ typically precede measurable weight change[4]. These findings support the utility of indirect calorimetry not only as a tool for metabolic phenotyping but also as a dynamic pharmacodynamic marker in early-phase drug development.

UNIVERSAL EATING MONITOR: OBJECTIVE FOOD INTAKE MEASUREMENT

Physiological Mechanism:

The Universal Eating Monitor (UEM) is a laboratory-based tool designed to quantify real-time eating behavior. It typically consists of an electronically integrated scale connected to a computer that continuously records the weight of a food container during a meal. This allows for precise measurement of food intake patterns, including eating rate, cumulative intake, and meal termination behaviors. Unlike subjective measures such as self-reported hunger, the UEM provides direct, objective, and quantifiable insights into actual ingestive behavior.

Operational Notes:

The Universal Eating Monitor (UEM) enables continuous, real-time measurement of food intake behavior under controlled laboratory conditions. It uses an electronic scale connected to data acquisition software to quantify meal microstructure, including cumulative intake, eating rate, bite patterns, and meal duration. The meal is typically presented in a distraction-free, temperature-controlled environment, with the scale and monitoring system concealed from the participant to minimize reactivity bias.

The test meal should be uniform, bland, and presented in excess to avoid constraining intake. Participants are instructed to eat until comfortably full within a fixed observation window. Fluid intake and utensils are standardized to reduce variability. While the UEM was originally developed in academic settings, it can be implemented in early-phase trials with minimal infrastructure expansion, provided that procedures for meal preparation, serving, and environmental control are carefully standardized. Staff training and protocol adherence are essential to ensure the accuracy and reproducibility of intake data.

Rationale for Early Use:

Changes in eating behavior are among the earliest pharmacodynamic effects of appetite-modulating therapies. Reductions in ad libitum food intake, particularly when measured in a standardized laboratory environment, can occur after a single dose of certain agents. Because cumulative energy intake is a fundamental driver of weight change, early alterations in food consumption provide a strong indication of downstream efficacy. The UEM allows researchers to detect subtle and immediate effects on satiety, bite size, and meal pacing that may not be captured through questionnaires or delayed weight loss metrics.

Supporting Evidence:

The UEM has been widely used in early-phase studies to quantify reductions in energy intake. Blundell et al. used laboratory meal tests to demonstrate that semaglutide-treated subjects consumed approximately 24% fewer calories than placebo controls within 12 weeks, corresponding with significant reductions in body weight and fat mass [6]. These effects were observable in advance of maximal weight change and confirmed that reduced intake was a principal mechanism of action. Similarly, other studies employing the UEM have shown that therapies targeting hypothalamic or gastrointestinal satiety pathways lead to measurable intake reductions within days, validating the UEM's use as a sensitive and early behavioral endpoint[7]. In a three-way crossover study presented at the AHPPI Winter Meeting, a single dose of sibutramine (15 or 30 mg) resulted in statistically significant reductions in food intake compared to placebo, as measured by the UEM within the same-day observation window[8].

GUT HORMONES: GLP-1, PYY, AND RELATED PEPTIDES

Physiological Mechanism:

Glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) are anorexigenic hormones secreted by enteroendocrine L-cells in the distal small intestine and colon in response to nutrient intake. These hormones act on central and peripheral targets to reduce appetite, slow gastric emptying, and promote satiety. GLP-1 receptor agonists (GLP-1 RAs), such as semaglutide, mimic this effect pharmacologically and have demonstrated robust efficacy in promoting weight loss. PYY, particularly the 3-36 isoform, contributes to meal termination through hypothalamic signaling and may have additive or synergistic effects when elevated alongside GLP-1.

Operational Notes:

Postprandial gut hormones such as GLP-1 and PYY are typically measured in plasma samples collected before and after a standardized meal or nutrient challenge. These assays require careful attention to timing relative to food intake and dosing, as secretion patterns are highly dynamic and peak concentrations occur within minutes to an hour following nutrient exposure. To preserve peptide stability, blood samples should be collected using tubes containing appropriate protease inhibitors, kept on ice, and processed promptly through centrifugation and plasma separation before freezing.

Measurement can be performed by central laboratories using validated immunoassays or multiplex platforms. While not universally implemented in early-phase trials, these assessments can be integrated feasibly when protocols are developed with predefined sampling windows and staff are trained in sample handling and processing requirements. Accurate interpretation of gut hormone data depends on consistent pre-analytical conditions and clear documentation of nutrient stimuli, meal timing, and assay specifications.

Rationale for Early Use:

Because gut hormone secretion changes rapidly in response to nutrient and pharmacologic stimuli, circulating levels of GLP-1 and PYY can serve as early indicators of satiety pathway engagement. For agents intended to modulate appetite, either through direct receptor agonism or through indirect mechanisms such as altered nutrient transit, early increases in postprandial GLP-1 or PYY suggest biological activity. Although GLP-1 is often administered as a therapeutic agent, endogenous GLP-1 levels may still serve as informative

biomarkers, particularly when the mechanism of action is upstream or modulates nutrient sensing indirectly. Measuring these hormones in early-phase trials, for example through timed pre- and post-meal plasma concentrations, offers an opportunity to confirm target engagement, anticipate intake reductions, and forecast treatment durability.

Supporting Evidence:

GLP-1 and PYY responses have been extensively studied in both surgical and pharmacologic models of weight loss. For example, van Bloemendaal et al. showed that exogenous GLP-1 administration reduced appetite and food intake in both lean and obese individuals[9]. Endogenous hormone responses are also predictive: individuals with higher postprandial GLP-1 and PYY levels following bariatric surgery exhibit more substantial weight loss and improved metabolic outcomes[10]. These findings suggest that therapies that evoke early and sustained increases in these hormones may be more likely to produce long-term weight reduction. Consequently, GLP-1 and PYY represent both mechanistic effectors and measurable biomarkers of appetite suppression.

BODY COMPOSITION TECHNIQUES: DEXA AND MRI

Physiological Mechanism:

Traditional measures of weight do not distinguish between fat mass, lean mass, bone, or fluid shifts. This limits their utility in short-duration trials where small but meaningful changes in adiposity may not be reflected on the scale. Dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI) are validated techniques that can noninvasively quantify fat mass, lean tissue, and fat distribution. However, these methods differ in their ability to assess adipose compartmentalization. DEXA provides high precision for total and regional fat mass but offers limited insight into specific fat depots. In contrast, MRI enables visualization and quantification of fat within pathogenic compartments such as visceral, ectopic (e.g., hepatic), or intramuscular stores. These compartments are more strongly associated with cardiometabolic risk than subcutaneous fat, making MRI particularly valuable when therapeutic effects are expected to impact these high-risk depots. As such, MRI and DEXA may serve complementary roles depending on the mechanistic target and clinical objectives of a given study.

Operational Notes:

Dual-energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI) are noninvasive imaging techniques commonly used to assess body composition in clinical research. DEXA provides rapid, low-burden quantification of total and regional fat mass, lean mass, and bone mineral content. It is widely available and relatively easy to integrate into early-phase trials, particularly when centralized reading and quality control procedures are in place.

MRI offers more detailed visualization of fat compartmentalization, including quantification of visceral, hepatic, and intramuscular adipose depots that are not well resolved by DEXA. MRI protocols must be standardized for sequence selection, positioning, and analysis, and require greater coordination between clinical and imaging teams (including radiology). When used appropriately, MRI provides valuable insight into tissue-specific effects that may be associated with cardiometabolic risk reduction.

Selection between DEXA and MRI should be based on the therapeutic mechanism of interest, site capability, and the level of resolution required to evaluate the pharmacodynamic response.

Rationale for Early Use:

In early-phase trials, a treatment that preferentially reduces fat mass or improves body composition may not produce significant weight loss within the study period, particularly if lean mass is preserved or increased. DEXA allows for the precise quantification of total and regional fat and lean mass, making it a valuable tool when monitoring changes in overall body composition. However, DEXA offers limited insight into the location or biological relevance of specific fat depots. In

contrast, MRI can distinguish and quantify fat within compartments that are more strongly linked to adverse metabolic outcomes, such as visceral, hepatic, and intramuscular fat. These depots are known to exert greater pathogenic influence compared to subcutaneous adipose tissue. When therapeutic effects are expected to impact these high-risk compartments, MRI provides more detailed and clinically meaningful information. Selection between these imaging modalities should reflect the intervention's mechanism of action and the trial's objectives.

Supporting Evidence:

Heymsfield et al. reviewed imaging modalities for body composition analysis and concluded that both DEXA and MRI are sensitive to early, small changes in fat mass[2]. For example, decreases in liver fat content measured by MRI have been observed within two to six weeks of initiating a very low-calorie diet and may precede observable changes in body weight[11]. These early shifts in ectopic fat are associated with improvements in insulin sensitivity and glycemic control. Similarly, DEXA-based studies have shown that reductions in total fat mass as small as 1 to 2 percent can be detected within 4 to 6 weeks and may predict overall treatment success. In clinical pharmacology, these modalities provide critical insight into tissue-level responses that are not captured by weight measurements alone, supporting their inclusion as pharmacodynamic endpoints in early-phase development.

DISCUSSION

The five pharmacodynamic models described in this review offer complementary, physiologically grounded methods for evaluating early indicators of weight-loss efficacy. Each provides distinct insight into a specific mechanistic domain: substrate utilization (ketones, RQ), energy balance (REE), ingestive behavior (UEM), hormonal regulation of appetite (GLP-1, PYY), and tissue-level outcomes (DEXA, MRI). Together, they form a toolkit for characterizing the pharmacodynamic profile of weight-loss interventions well before changes in total body weight are evident.

INTEGRATION AND PREDICTIVE VALUE

When used in combination, these markers can offer a multi-dimensional profile of a treatment's biological activity. For instance, a decrease in RQ alongside a reduction in ad libitum energy intake and an increase in PYY levels provides convergent evidence of negative energy balance and appetite suppression. Such consistency across domains strengthens confidence in early efficacy and enhances signal detection in small, short-duration trials. While no single biomarker is perfectly predictive, a convergent pattern can improve forecasting accuracy and inform go/no-go decisions.

ACCELERATION OF PROOF-OF-CONCEPT

Incorporating plausibly mechanistic pharmacodynamic endpoints into Phase I or II trials can provide early insight into whether a treatment is engaging its intended biological targets and producing measurable effects consistent with weight-loss efficacy. These early signals can support internal decision making by informing dose selection, prioritization of candidates, or refinement of study design, without requiring long-term changes in body weight as the sole indicator of progress. While these PD models are not intended to replace primary efficacy endpoints, they can serve as valuable tools for enhancing the strategic value of early-phase trials.

INTERPRETIVE NUANCES AND LIMITATIONS

While promising, early PD markers require careful interpretation. Biological variability, diurnal rhythms, and context-specific confounders (e.g., recent dietary intake, hydration status) must be controlled. For calorimetry, pre-test fasting and environmental standardization are essential. For hormone assays, timing relative to meals is critical. Additionally, not all PD responses are durable: transient increases in GLP-1 or reductions in RQ may not persist and thus may not correspond to sustained weight loss. These limitations underscore

the need for repeated measures and parallel clinical assessments when using PD endpoints for decision-making.

Practical Considerations for Implementation

While the pharmacodynamic models described offer clear conceptual value, their successful deployment in early-phase clinical trials depends on careful operational planning, standardization, and attention to logistical feasibility.

Feasibility in Early-Phase Settings

Most early-phase clinical pharmacology units are equipped to implement blood-based biomarker collection (e.g., for ketones, GLP-1, and PYY) and indirect calorimetry, provided appropriate staff training and quality control measures are in place. DEXA scanning is widely available, rapid, and cost-effective, with minimal radiation exposure, making it a practical option even in small trials. MRI, while more resource-intensive, may be justified when mechanistic insight into regional fat depots (e.g., hepatic or visceral fat) is central to the drug's purported mechanism of action. The Universal Eating Monitor, while requiring specialized setup, can often be implemented with minimal operational expansion if appropriately standardized.

Standardization and Timing

For all PD markers, consistent timing relative to meals, dosing, and circadian variation is critical. For example, GLP-1 and PYY assays require specific sample handling protocols, including the use of protease inhibitors and rapid cold centrifugation, to ensure analyte stability. Indirect calorimetry should be conducted under thermoneutral, fasting conditions using standardized equipment and protocols. Pre-test dietary control may be necessary to reduce inter-individual variability in respiratory quotient. Similarly, ad libitum meal testing using UEM or equivalent methods must standardize meal composition, serving temperature, and environmental conditions.

Data Interpretation and Strategic Value

Interpretation of early pharmacodynamic responses should emphasize within-subject changes from baseline and, where feasible, comparisons to placebo. Single time-point assessments are discouraged, as they may not capture the trajectory or durability of effect. Repeated measurements over the first 2 to 6 weeks of treatment are recommended to improve signal reliability and assess consistency across time. While these markers are not intended to serve as primary efficacy endpoints, they can provide important context for understanding treatment effects, informing dose refinement, and supporting go/no-go decisions. Clear documentation of sampling methods, assay conditions, and timing relative to dosing and meals enhances the interpretability and reproducibility of findings, especially when comparing results across compounds or programs.

Patient Experience and Acceptability

The feasibility of pharmacodynamic assessments should take into account participant experience, particularly when procedures are repeated over time. In early-phase mechanistic trials, where participants are typically closely monitored in controlled settings, procedures such as fasting blood collection, calorimetry, or imaging are generally well tolerated when implemented with appropriate scheduling and support. Protocols should aim to minimize procedural redundancy and ensure that study designs are not unnecessarily complex, especially when multiple PD modalities are used in parallel. Clear communication of study expectations and alignment with participant preferences can help maintain engagement and compliance. With thoughtful planning, even intensive pharmacodynamic assessments can be integrated effectively into early-phase trial workflows.

Triangulation Across Domains

Drug developers may derive the greatest strategic value from implementing two or more pharmacodynamic models in parallel, particularly when those models reflect distinct but converging mechanistic domains. For example, combining indirect calorimetry (reflecting substrate utilization

and energy expenditure) with DEXA or MRI (providing tissue-level resolution of fat mass changes) can help distinguish whether early metabolic shifts are being driven primarily by thermogenesis or changes in intake behavior. Similarly, pairing behavioral assessments such as ad libitum intake monitoring with circulating satiety hormone measurements may clarify the neuroendocrine basis for observed appetite changes. Triangulating across these domains improves confidence in early signals by demonstrating physiological consistency and may help guide decisions about dose selection, cohort expansion, or pipeline prioritization. While each PD measure contributes unique information, convergence across modalities strengthens the interpretive power of early-phase data.

CONCLUSION

Pharmacodynamic biomarkers offer an important opportunity to enhance early-phase obesity drug development by providing timely, physiologically meaningful evidence of biological activity. When reductions in body weight are not yet discernible, markers such as β-hydroxybutyrate, respiratory quotient, objective food intake, postprandial satiety hormones, and regional fat mass shifts can help determine whether a treatment is producing physiologic effects consistent with eventual weight loss.

This white paper has synthesized findings from a narrative review of five major pharmacodynamic models. Each was selected based on its mechanistic plausibility, early detectability, and supporting evidence of relevance to long-term weight outcomes. While no single marker is sufficient on its own, these models can be used in combination to generate a cohesive and interpretable profile of early therapeutic activity. When implemented thoughtfully, these tools can inform development-stage prioritization, guide dose refinement, and support go/no-go decisions.

Realizing the full utility of these tools depends on thoughtful implementation and data integrity. When integrated with care, pharmacodynamic assessments can provide consistent, actionable insights within the limited duration of early-phase trials. Pharmacodynamic endpoints should be prospectively defined and scientifically justified, with integration into protocol design and statistical planning from the outset.

As the field of obesity pharmacotherapy continues to expand, there will be an increasing need for pharmacodynamic methods that can differentiate mechanisms, inform go/no-go decisions, and support rational development strategies. Pharmacodynamic models such as those described in this review can help meet that need by offering insight well before weight loss is measurable, ultimately strengthening the scientific foundation of early-stage trials and improving overall development efficiency.

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We also acknowledge the peer-reviewed scientific literature that provided the empirical foundation for this review. Although this paper was not based on a structured systematic review, great care was taken to ensure the inclusion of high-quality, verifiable references from reputable journals and data sources.

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