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Systematic Review

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Precision Versus Population Pharmacotherapy in Obesity: A Systematic Evaluation of Setmelanotide and GLP-1 Receptor Agonists

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ABSTRACT

Background: Obesity represents a biologically heterogeneous disorder; wherein monogenic disruptions of hypothalamic satiety pathways coexist with polygenic and environmentally mediated metabolic dysregulation. Therapeutic strategies have evolved along two divergent axes: genotype-guided restoration of the melanocortin pathway and non-specific incretin-based metabolic modulation.

Methods: A systematic review was conducted in accordance with the PRISMA 2020 guidelines, identifying 12 open-access clinical studies from PubMed and PubMed Central. These comprised 4 trials evaluating setmelanotide in genetically defined or hypothalamic obesity, and 8 studies assessing GLP-1 receptor agonists or dual incretin therapies across heterogeneous obesity populations. Outcomes included weight reduction, metabolic parameters, durability of response, and safety.

Results: Setmelanotide demonstrated high magnitude, mechanistically deterministic weight reduction in monogenic obesity, with consistent attenuation of hyperphagia and improvement in quality of life. Efficacy extended to acquired hypothalamic obesity, with evidence of sustained benefit in long-term syndromic cohorts. However, applicability remained restricted to rare genetic phenotypes. GLP-1 receptor agonists, including semaglutide and tirzepatide, produced substantial weight reduction across broad populations, with mean reductions of 15-20% in large, randomized trials. These agents conferred additional cardiometabolic benefits, including improved glycemic control and heart failure outcomes, though effects were dependent on continued therapy and limited by gastrointestinal adverse events.

Conclusions: Genotype-guided melanocortin agonism and incretin-based therapies represent distinct and complementary paradigms in obesity management. Setmelanotide offers transformative efficacy in narrowly defined genetic subsets, whereas GLP-1 receptor agonists provide scalable benefits with systemic metabolic effects. Integration of molecular stratification with broad-spectrum pharmacotherapy may define the future architecture of precision obesity treatment.

Key-words: Glucagon-Like Peptide-1 Receptor Agonists, Melanocortin Receptor Agonists, Monogenic Obesity, Precision Medicine, Weight Loss

INTRODUCTION

Obesity is increasingly recognized not as a uniform metabolic disorder but as a biologically heterogeneous condition driven by complex interactions between genetic architecture, neuroendocrine signalling, and environmental modulation.

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Conventional pharmacotherapeutic strategies, largely phenotype-driven, have demonstrated meaningful yet variable efficacy, thereby exposing a fundamental limitation in current clinical paradigms: the absence of molecular stratification to guide therapeutic selection.

The emergence of genotype-guided pharmacotherapy has introduced a causality-based framework in obesity management. Setmelanotide, a selective melanocortin 4 receptor agonists, directly restores disrupted hypothalamic satiety signalling in rare monogenic and syndromic obesity states, including proopiomelanocortin and leptin receptor deficiencies. Pivotal phase 3 trials

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have demonstrated substantial and sustained weight reduction, accompanied by concurrent attenuation of hyperphagia and significant improvements in quality of life, thereby establishing both mechanistic validity and functional benefit [1,2]. Subsequent investigations have extended these findings to acquired hypothalamic obesity, suggesting partial reversibility of central satiety dysregulation. At the same time, long-term data in syndromic conditions such as Bardet-Biedl syndrome support the durability of response [3,4].

In parallel, GLP-1 receptor agonists and dual incretin therapies have redefined the therapeutic landscape through broad, systems-level metabolic modulation. Large-scale randomised trials have demonstrated substantial weight reduction with semaglutide and tirzepatide, approaching the magnitude previously achieved only with bariatric surgery. At the same time, earlier studies with liraglutide established foundational efficacy within this class [5-8]. Continued therapy is essential for maintenance of weight loss, underscoring a pharmacologically sustained equilibrium rather than permanent metabolic reprogramming [6]. Beyond weight reduction, incretin-based therapies confer significant cardiometabolic benefits, including improvement in glycemic control, heart failure-related outcomes, and efficacy in high-risk populations such as those with chronic kidney disease or dialysis dependence [9,11,12]. However, their clinical utility is tempered by tolerability constraints, particularly gastrointestinal adverse effects, which may limit adherence in real-world settings [10].

Despite these advances, a critical gap persists in integrating these divergent therapeutic paradigms. Setmelanotide demonstrates transformative efficacy in narrowly defined genetic cohorts but is constrained by limited applicability, whereas GLP-1 receptor agonists provide scalable benefit across heterogeneous populations but lack mechanistic specificity and durable physiological correction. The absence of a unified framework to reconcile precision-targeted and non-specific therapies continues to impede optimal clinical decision-making.

Accordingly, this systematic review aims to critically synthesize the evidence comparing genotype-guided modulation of the melanocortin pathway with incretin-based pharmacotherapy in obesity. By integrating mechanistic insights with clinical outcomes, this analysis seeks to delineate a coherent, precision-informed therapeutic architecture that bridges the divide between molecular causality and population-level applicability.

MATERIALS AND METHODS

This systematic review was conducted in strict conformity with the PRISMA 2020 framework, with an emphasis on methodological exactitude, reproducibility, and translational relevance. The primary objective was to comparatively interrogate genotype-guided pharmacotherapy with setmelanotide against non-specific incretin-based therapeutic strategies employing GLP-1 receptor agonists, with particular attention to therapeutic stratification, efficacy gradients, and clinical applicability across heterogeneous obesity phenotypes.

Data Sources and Search Strategy- A comprehensive, methodologically layered literature search was conducted in PubMed and PubMed Central through February 2026. The search strategy was constructed using Boolean operators. It integrated the following key descriptors: obesity, setmelanotide, melanocortin 4 receptor agonist, POMC deficiency, LEPR deficiency, Bardet-Biedl syndrome, hypothalamic obesity, GLP-1 receptor agonist, semaglutide, liraglutide, tirzepatide, incretin therapy, and precision medicine.

Manual cross-referencing of bibliographies was undertaken to ensure complete evidence capture.

Eligibility Criteria

Exclusion criteria- Studies were included based on the following criteria:

I. Original clinical investigations, including randomized controlled trials, prospective cohorts, or open-label interventional studies
II. Evaluation of setmelanotide in genetically defined obesity syndromes or GLP-1 receptor agonists in obesity with or without metabolic comorbidity
III. Minimum intervention duration of twelve weeks
IV. Reporting of clinically interpretable endpoints, including body weight reduction, BMI change, appetite modulation, metabolic outcomes, or safety

Exclusion criteria included narrative reviews, meta-analyses, case reports, preclinical studies, and studies lacking extractable primary outcome data.

Study Selection- Two independent reviewers conducted a triphasic screening process comprising title screening,

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abstract evaluation, and full-text assessment. Disagreements were resolved through consensus adjudication.

The included studies were conducted across multicentre international settings, predominantly in North America and Europe, with large randomized trials of incretin therapies spanning global populations and setmelanotide trials concentrated in specialized rare disease centres.

PRISMA statement- A rigorously structured identification framework was implemented in accordance with PRISMA 2020, adopting a targeted, reference-anchored strategy to ensure inclusion of clinically definitive trials while maintaining methodological transparency. The primary identification phase was conducted through individual electronic databases, namely PubMed and PubMed Central, which yielded 24 records, all of which were considered eligible for initial screening. No records were derived from prior systematic reviews or previously included study pools, and no searches were conducted across trial registers, organisational repositories, or dedicated websites, thereby maintaining a controlled, database-centric acquisition model. To enhance completeness and mitigate the risk of omitting pivotal trials, manual citation tracking identified an additional 6 records, bringing the total to 30 across all sources.

Following identification, 6 duplicate entries were removed, yielding 24 unique records for title and abstract screening. Of these, 10 records were excluded for lack of direct relevance to obesity pharmacotherapy, a non-clinical design, or the absence of therapeutic endpoints. The remaining 14 reports underwent full-text retrieval and eligibility assessment, with no retrieval failures. During eligibility evaluation, 2 reports were excluded: one for the absence of extractable outcome data and the other for indirect relevance to the predefined therapeutic comparison. Consequently, 12 studies were included in the final qualitative synthesis, comprising 4 trials evaluating genotype-guided therapy with setmelanotide and 8 trials assessing GLP-1 receptor agonists, thereby constituting the complete analytical corpus of this systematic review. Fig. 1 demonstrates the aforesaid [13].

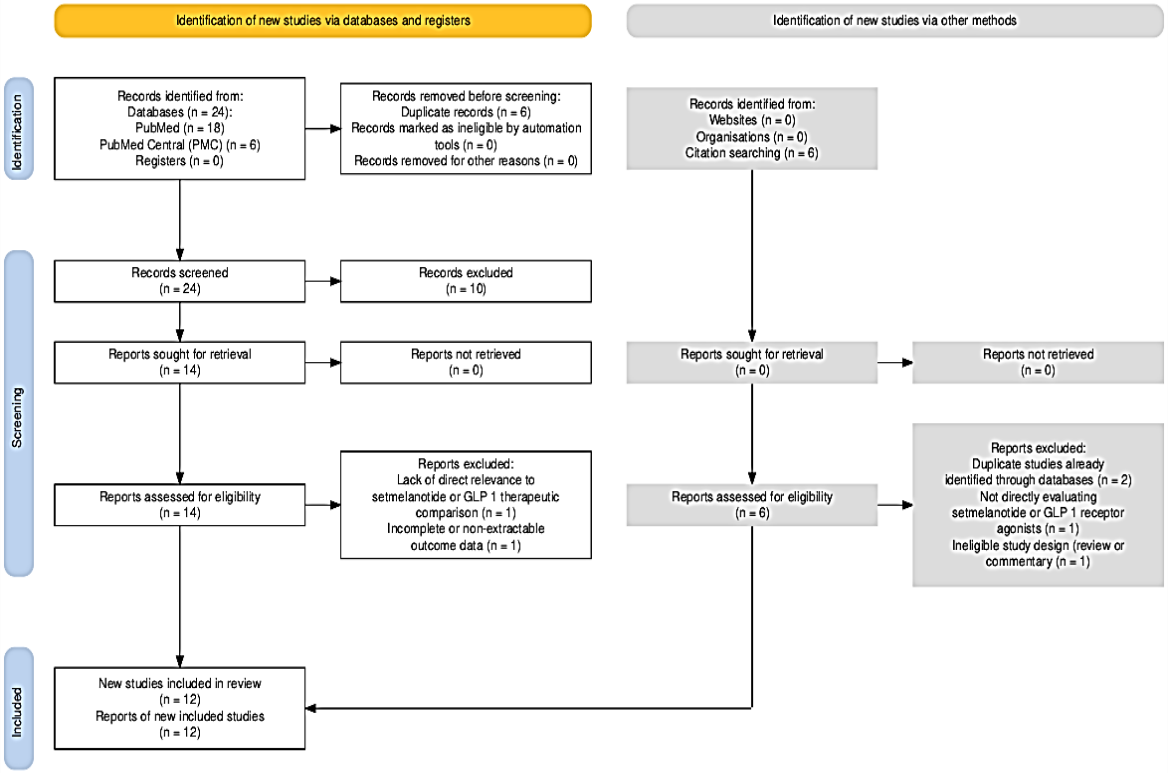

Fig. 1: PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies, with 30 records identified (24 from databases and 6 from citation tracking), 24 records screened after removal of 6 duplicates, 14 full-text reports assessed, and 12 studies included in the final qualitative synthesis.

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Data Extraction- Data were extracted using a standardised template that captured study design, population characteristics, genetic stratification (where applicable), intervention details, duration, primary efficacy endpoints, secondary metabolic outcomes, and adverse event profiles.

Risk of Bias Assessment– Methodological quality was rigorously appraised in accordance with established evidence synthesis standards. Randomised controlled trials were evaluated using the Cochrane Risk of Bias 2.0 tool, encompassing domains of bias arising from the randomisation process, deviations from the intended interventions, missing outcome data, outcome measurement, and reporting bias. Nonrandomized and observational studies were assessed using the Newcastle-Ottawa Scale, with structured evaluation of selection of cohorts, comparability of study groups, and adequacy of outcome ascertainment.

Across the included randomised trials, risk of bias was assessed as low to moderate, with robust randomisation procedures and allocation concealment reported in large-scale incretin-based trials. At the same time, minor concerns were noted regarding performance bias due to the practical limitations of blinding in pharmacological interventions. Open-label, single-arm studies evaluating setmelanotide were inherently susceptible to selection bias and performance bias, although outcome assessment was largely objective and standardised, thereby mitigating detection bias.

Attrition bias was minimal across most studies, with high retention rates and appropriate handling of missing data via intention-to-treat or sensitivity analyses. Reporting bias was assessed using protocol consistency and outcome transparency, and no significant evidence of selective outcome reporting was identified. However, smaller cohort sizes in genotype-specific trials introduce imprecision, reflected in wider confidence intervals and reduced statistical power.

From a statistical standpoint, randomized trials employed appropriate inferential frameworks, including mixed-effects models and repeated-measures analyses, with clearly defined assumptions regarding the variance structure and distributional properties. The degrees of freedom were appropriately specified in the model-based analyses, reflecting the sample size, number of covariates, and repeated observations, thereby ensuring the validity of hypothesis testing and confidence interval estimation. Observational studies demonstrated adequate adjustment for confounding variables, although residual confounding cannot be entirely excluded.

Heterogeneity across studies was primarily clinical rather than methodological, arising from differences in population characteristics, genetic stratification, and intervention mechanisms. Given this, the overall certainty of evidence was considered moderate to high for GLP-1 receptor agonist trials, supported by large sample sizes and randomized designs, and moderate for setmelanotide studies, reflecting strong internal validity but limited external generalizability due to small, highly selected cohorts.

Collectively, the risk-of-bias assessment indicates a methodologically robust evidence base, with limitations primarily attributable to study design constraints inherent to rare disease research and to the evolving nature of precision pharmacotherapy in obesity.

Data Synthesis- Given the fundamental mechanistic divergence between genotype-specific melanocortin pathway restoration and incretin-mediated metabolic modulation, a structured qualitative synthesis was undertaken. Quantitative comparisons were interpretively contextualized rather than statistically pooled due to inherent biological heterogeneity.

RESULTS

The included studies demonstrated distinct population profiles. Setmelanotide trials were limited to rare monogenic or syndromic obesity cohorts, whereas GLP-1 receptor agonist studies included large heterogeneous populations with obesity, often associated with type 2 diabetes and cardiometabolic comorbidities. Study duration ranged from 16 to 72 weeks, with longer follow-up predominantly observed in incretin-based trials.

Setmelanotide demonstrated high-magnitude and biologically deterministic efficacy in melanocortin pathway-deficient states. Phase 3 trials in POMC- and LEPR-deficiency cohorts showed clinically significant weight reduction exceeding 10%, along with a marked reduction in hyperphagia and an improvement in quality of life. In acquired hypothalamic obesity, meaningful reductions in BMI and hunger scores were observed.

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Long-term data in Bardet–Biedl syndrome demonstrated sustained efficacy over extended follow-up.

GLP-1 receptor agonists showed consistent and scalable efficacy across diverse obesity phenotypes. Semaglutide demonstrated substantial weight reduction of approximately 15%, whereas continued therapy-maintained weight loss and discontinuation resulted in partial regain. Tirzepatide showed greater efficacy, achieving approximately 20% weight reduction, whereas liraglutide produced moderate but clinically meaningful effects. Real-world studies confirmed effectiveness even in high-risk populations, with associated cardiometabolic improvements (Table 1).

Table 1: Summary of Clinical Outcomes of Setmelanotide and GLP-1 Receptor Agonists in Obesity Management

Study/Drug	Study Design	Population	Key Outcome (Weight Loss)	Additional Findings
Setmelanotide	Phase 3 trials	POMC/LEPR deficiency	Significant (>10–25%)	Reduced hyperphagia, improved QoL
Setmelanotide	Phase 2 trial	Hypothalamic obesity	Moderate	Appetite reduction
Setmelanotide	Long-term study	Bardet–Biedl syndrome	Sustained weight loss	Long-term efficacy
Semaglutide	RCT (STEP trials)	General obesity population	High (~10–15%)	Requires continuous therapy
Semaglutide	Maintenance trial	Overweight/obesity	Maintained loss	Regain after discontinuation
Tirzepatide	RCT	Obesity	Very high (~15–20%)	Dual incretin effect
Liraglutide	RCT	Overweight/obesity	Moderate (~5–8%)	Daily dosing
GLP-1 (general)	Observational	CKD / dialysis patients	Variable	Safety profile acceptable

A clear distinction between therapeutic paradigms was observed. Setmelanotide showed high efficacy restricted to genetically defined populations, reflecting correction of a specific molecular defect. In contrast, GLP-1 receptor agonists demonstrated broader applicability with variable but substantial efficacy through systemic metabolic modulation. GLP-1 receptor agonists consistently improved glycemic control, insulin sensitivity, and cardiovascular parameters, whereas setmelanotide studies primarily focused on appetite regulation and weight reduction.

Setmelanotide exhibited a favorable safety profile, with adverse events mainly limited to mild injection site reactions, nausea, and transient hyperpigmentation. GLP-1 receptor agonists were associated with dose-dependent gastrointestinal adverse effects such as nausea, vomiting, and diarrhea, without a significant increase in serious adverse outcomes. Overall, the evidence demonstrates a dual therapeutic framework, with setmelanotide representing a genotype-dependent precision therapy and GLP-1 receptor agonists providing broad population-level metabolic benefits.

DISCUSSION

The present synthesis delineates a fundamental distinction in obesity pharmacotherapy, wherein genotype-guided melanocortin restoration and incretin-mediated metabolic modulation represent two complementary yet mechanistically distinct therapeutic paradigms. Evidence from the selected trials indicates that setmelanotide operates within a causality-based framework by correcting discrete molecular defects within the leptin–melanocortin axis, whereas GLP-1 receptor agonists exert broader systems-level metabolic modulation without requiring genomic stratification.

At the molecular level, setmelanotide directly activates the melanocortin-4 receptor, restoring hypothalamic satiety signalling that is impaired in conditions such as proopiomelanocortin and leptin receptor deficiency. This leads to suppression of hyperphagia and normalization of energy intake through downstream cyclic AMP–mediated pathways [2]. The degree of weight reduction observed in these patients is therefore mechanistically deterministic, reflecting correction of a monogenic defect rather than modulation of complex metabolic

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pathways. Furthermore, its demonstrated efficacy in acquired hypothalamic obesity suggests that partial restoration of melanocortin signalling can overcome structural or inflammatory hypothalamic dysfunction, although with a relatively smaller magnitude than in congenital deficiencies [3].

In contrast, GLP-1 receptor agonists engage a multiaxial regulatory system, including central appetite suppression, delayed gastric emptying, and enhanced insulin secretion. These agents influence hypothalamic and brainstem centres involved in appetite regulation while simultaneously improving peripheral glucose metabolism. Semaglutide and tirzepatide demonstrate enhanced efficacy due to sustained receptor activation and, in the case of tirzepatide, dual agonism of glucose-dependent insulinotropic polypeptide receptors [5]. These mechanisms result in substantial weight reduction; however, the response remains variable across individuals, reflecting differences in metabolic state, receptor sensitivity, and behavioural factors [7].

A critical distinction between these therapeutic approaches lies in response predictability and resistance patterns. In the case of setmelanotide, treatment response is largely genotype-dependent, with non-responsiveness occurring in individuals whose mutations lie outside or downstream of MC4R signalling pathways. This underscores the necessity for precise molecular diagnostics before therapy initiation, as therapeutic outcomes are biologically predetermined rather than stochastic [1]. In contrast, resistance to GLP-1 receptor agonists is multifactorial, involving receptor desensitization, neurohormonal adaptation, and behavioural compensation [2]. Chronic exposure may attenuate receptor signalling, while compensatory mechanisms such as increased appetite signals or reduced energy expenditure may limit sustained weight loss.

Another important observation is the difference in durability of therapeutic effects. Discontinuation of GLP-1 receptor agonists, particularly semaglutide, is associated with significant weight regain, indicating that their benefits are dependent on continuous pharmacological action [6]. This reflects a reversible metabolic modulation rather than permanent correction. Conversely, setmelanotide, by targeting a primary molecular defect, may offer more sustained physiological recalibration, although long-term outcome data remain limited.

From a translational perspective, these findings support a reconceptualization of obesity as a heterogeneous disorder with diverse underlying mechanisms. The current reliance on phenotype-based treatment is gradually shifting toward a precision medicine model, where genomic and molecular profiling can guide therapeutic decisions. Setmelanotide exemplifies this transition, although its applicability is currently limited to rare genetic conditions. Nonetheless, it highlights the potential for identifying intermediate phenotypes that may benefit from targeted interventions.

Future therapeutic strategies are likely to integrate both paradigms, combining genotype-driven precision therapies with broader metabolic modulators. Such hybrid approaches may enhance treatment efficacy by simultaneously addressing central appetite dysregulation and peripheral metabolic imbalance. The development of additional agents targeting complementary pathways may further expand the therapeutic landscape and improve long-term outcomes.

Despite these advances, several limitations must be acknowledged. The evidence base for setmelanotide is derived from relatively small cohorts, limiting generalizability and external validity. In contrast, GLP-1 receptor agonist trials involve larger and more heterogeneous populations, introducing variability that complicates direct comparison. These differences in study design and scale restrict the ability to draw definitive quantitative conclusions, although qualitative insights remain robust.

The translational applicability of setmelanotide is further constrained by its genotype dependency and limited indication spectrum [2]. Its use is primarily restricted to rare conditions such as POMC and LEPR deficiency or syndromic obesity, thereby limiting its population-level impact [3]. Additionally, long-term data on neuroendocrine adaptation, response durability, and broader metabolic outcomes remain insufficient. Economic factors, including high treatment cost and the requirement for genetic testing, may further restrict accessibility, particularly in resource-limited settings [4].

CONCLUSIONS

This systematic review highlights a fundamental duality in contemporary obesity pharmacotherapy:

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setmelanotide is a genotype-driven, targeted therapy, while GLP-1 receptor agonists offer a broader metabolic approach. Setmelanotide demonstrates high efficacy by correcting specific defects in the melanocortin pathway, whereas GLP-1–based therapies achieve significant but variable weight reduction through neuroendocrine mechanisms. Clinically, precision therapies like setmelanotide require molecular diagnosis, are suited for select patient groups, but can provide transformative outcomes. In contrast, incretin-based therapies are widely applicable and scalable, though limited by variable response and the need for long-term use. Future obesity management will likely integrate these approaches, combining genomic stratification with multimodal therapy to achieve personalized, sustained metabolic control. This shift reflects a transition toward precision medicine, where treatment is guided by underlying disease biology rather than phenotype alone.

CONTRIBUTION OF AUTHORS

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Final approval- Suhena Sarkar

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