

Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic

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Objective: Little is known about the predictors of response to obesity interventions.

Methods: In 450 participants with obesity, body composition, resting energy expenditure, satiety, satiation, eating behavior, affect, and physical activity were measured by validated studies and questionnaires. These variables were used to classify obesity phenotypes. Subsequently, in a 12-month, pragmatic, real-world trial performed in a weight management center, 312 patients were randomly assigned to phenotype-guided treatment or non-phenotype-guided treatment with antiobesity medications: phentermine, phentermine/topiramate, bupropion/naltrexone, lorcaserin, and liraglutide. The primary outcome was weight loss at 12 months.

Results: Four phenotypes of obesity were identified in 383 of 450 participants (85%): hungry brain (abnormal satiation), emotional hunger (hedonic eating), hungry gut (abnormal satiety), and slow burn (decreased metabolic rate). In 15% of participants, no phenotype was identified. Two or more phenotypes were identified in 27% of patients. In the pragmatic clinical trial, the phenotype-guided approach was associated with 1.75-fold greater weight loss after 12 months with mean weight loss of 15.9% compared with 9.0% in the non-phenotype-guided group (difference -6.9% [95% CI -9.4% to -4.5%], $P < 0.001$), and the proportion of patients who lost >10% at 12 months was 79% in the phenotype-guided group compared with 34% with non-phenotype-guided treatment group.

Conclusions: Biological and behavioral phenotypes elucidate human obesity heterogeneity and can be targeted pharmacologically to enhance weight loss.

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Introduction

Obesity is a chronic, relapsing, multifactorial disease (1), the prevalence of which continues to increase worldwide (2). The complexities of obesity result in redundant, adaptive mechanisms to preserve energy (1); consequently, obesity is a remarkably heterogeneous disease, and sustained weight loss with current treatment paradigms remains a challenge in clinical practice (3,4). The heterogeneity among patients with obesity is particularly apparent in the varied weight loss response to obesity interventions, such as diets, medications, devices, and surgery (1).

Study Importance

What is already known?

- Obesity is a chronic, relapsing, multifactorial disease, the prevalence of which continues to increase worldwide. Obesity is a remarkably heterogeneous disease, and sustained weight loss with current treatment paradigms remains a challenge in clinical practice.
- The heterogeneity among patients with obesity is particularly apparent in weight loss response to obesity interventions, such as diets, medications, devices, and surgery.
- Little is currently known about the predictors of response to obesity interventions.

What does this study add?

- We stratified obesity into four phenotypes: hungry brain (abnormal satiation), emotional hunger (hedonic eating), hungry gut (abnormal satiety), and slow burn (decreased metabolic rate).
- In a clinical cohort prescribed antiobesity medication, the phenotype-guided approach was associated with 1.75-fold greater weight loss after 1 year, and the proportion of patients who lost >10% at 1 year was 79% compared with 34% with non-phenotype-guided treatment.

How might these results change the direction of research or the focus of clinical practice?

- We have identified actionable phenotypes of obesity based on pathophysiology and behavior that elucidate human obesity heterogeneity and can be targeted to enhance weight loss outcomes of pharmacotherapy.

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Thus, antiobesity medications (AOMs) have a variable weight loss response rate (1,5). In a network meta-analysis, the proportion of patients who lost more than 10% with AOMs ranged from 20% to 54% compared with placebo (9%), and weight loss at 1 year with AOMs ranged from 2.6 to 8.8 kg compared with placebo (5). Early response, defined as >5% weight loss in the first 3 months, is the only current predictor of long-term weight loss with AOMs (6,7). Thus, the current standard of care is for providers to initially select AOMs based on physician/patient preference, medication interactions, comorbidities, risk of potential adverse events, or insurance coverage (1,8,9). Other than identifying responders by trial and error (6,7), little is currently known about the predictors of response to obesity interventions (3).

Current obesity classifications based on BMI (10), abnormal waist circumference, metabolically abnormal obesity (11), or the obesity staging system (12) identify cardiometabolic disease and mortality risk. However, these severity-based classifications or staging systems predominantly address cardiometabolic risk and do not address pathophysiological or etiological heterogeneity of obesity (13–15). There is a critical need to develop a valid classification of obesity based on pathogenesis and to ascertain its utility in obesity management to improve outcomes (1,16). In fact, the National Institutes of Health (NIH) has recognized the need to identify predictors of response to obesity treatment as a key approach to successfully manage this epidemic. The NIH's initiative, titled "Accumulating Data to Optimally Predict Obesity Treatment Core Measures" (17), aims to collect data on behavioral, biological, environmental, and psychosocial variables to identify predictors of response (17). To date, interrogations of large databases from biobanks or clinical trials have not identified predictors of significantly improved clinical outcomes to treatment (3).

Obesity is a disease of energy balance dysregulation (1) (Figure 1A) that results in excessive storage of calories in the form of fat (1). With regard to energy intake, the key determinants of eating behavior are the homeostatic and hedonic drives to eat (18). Homeostatic eating behavior, mainly controlled by the brain-gut axis, involves hunger (desire to eat), satiation (calories needed to reach fullness), and satiety

(duration of fullness) (19). Hedonic eating behavior is the desire to eat to cope with positive or negative emotions (20,21). With regard to energy expenditure, the key drivers are resting energy expenditure (REE), nonexercise physical activity, and the thermogenic effect of food and exercise (22). It is essential to elucidate differences among patients in some of these measurable components of food intake and energy expenditure and to assess their potential for individualizing therapy for obesity.

We hypothesized that pathophysiological characterization elucidates obesity subgroups and enhances response to obesity pharmacotherapy. Our aim was to characterize the obesity phenotypes and to assess the efficacy of phenotype-guided AOMs compared with non-phenotype-guided pharmacotherapy. Our long-term goal is to develop a personalized approach to obesity management.

Methods

Study participants and phenotyping tests

We studied two separate cohorts: (1) obesity phenotype characterization and classification ($n=450$ participants) and (2) prospective, pragmatic trial of phenotype-guided AOMs ($n=84$ cases and 228 controls). The studies were approved by the Mayo Clinic Institutional Review Board, and all participants gave written informed consent.

Obesity phenotyping tests

Participants were recruited from the community by standard advertising, and all the tests were performed at the Mayo Clinic Clinical Research Trials Unit after an 8-hour fasting period. All methods used are described in detail in the online Supporting Information.

All participants completed the following validated tests:

1. Homeostatic eating behavior (18) was divided into three stages: hunger, satiation, and satiety.

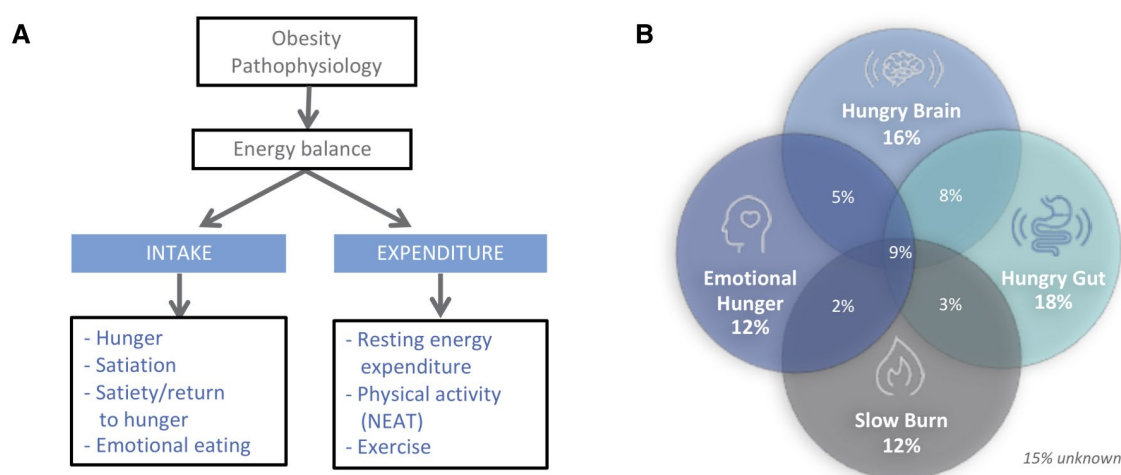


Figure 1 Pathophysiological classification of obesity. **(A)** Illustration of obesity pathophysiology based on energy balance and key components that contribute to human obesity. **(B)** Distribution of participants based on pathophysiological phenotypes in 450 patients with obesity (BMI > 30 kg/m²). NEAT, nonexercise activity thermogenesis.

- a Hunger, defined as desire to eat (23), studied by visual analog scale for hunger and desire to eat (100-mm scale) at baseline before breakfast and lunch.
 - b Satiation, defined as calories consumed to reach fullness and terminate meal (23), studied by ad libitum buffet meal (kilocalories consumed to reach maximal fullness) (24).
 - c Satiety, defined as duration of fullness or return of hunger (23), studied by visual analog scale for appetite (100-mm scale) at baseline and postprandially every 15 minutes for 2 hours after a standard 320-kcal meal (23,25) and by a quantifiable variable gastric emptying of solids that could impact both magnitude of postprandial fullness and time to return of hunger (26-28). Gastric emptying is summarized by the half-emptying time, $T_{1/2}$, in minutes.
2. Hedonic eating behavior (18) was assessed by the Hospital Anxiety and Depression Score (HADS) (26) and Three Factor Eating Questionnaire (TFEQ-21) (29); there is significant correlation between HADS and the emotional eating domain of the TFEQ-21 (30). Emotional eating was assessed by additional validated behavioral questionnaires (24,29,31).
 3. Energy expenditure was studied by REE (indirect calorimetry) (32), reported nonexercise physical activity, and reported exercise (33,34). Body composition was measured by dual-energy x-ray absorptiometry (35).

Obesity phenotype classification

Obesity phenotype classification was based on a cutoff of the 25th or 75th percentile of each measurement (applied separately for females and males) recorded in the first 100 participants who completed phenotype measurements (Table 1). The cutoffs were as follows: abnormal ad libitum buffet meal: 75th percentile for females >894 kcal and males >1,376 kcal, defined as “hungry brain”; abnormal behavioral questionnaire for anxiety: 75th percentile for both genders ≥ 7 points on HADS

scale, defined as “emotional hunger”; accelerated gastric emptying of the radiolabeled solid 320-kcal, 30% fat meal: 25th percentile for females <101 minutes and males <86 minutes, defined as “hungry gut”; and measured REE: 25th percentile for females <96% and males <94% of predicted REE based on Harris-Benedict equation, defined as “slow burn.” Visual analog scales for appetite were not considered in the classification because of small interindividual variability when measuring satiation and the lack of correlation with calories consumed, a more objective measurement. These cutoffs were applied in order to classify the phenotype(s) on the other 350 participants in the first study aim. See Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines checklist in online Supporting Information.

Phenotype-guided antiobesity pharmacotherapy

Patients with obesity were recruited between June 1, 2017, and June 30, 2019, for a comprehensive, prospective, pragmatic trial (36) of phenotype-guided AOMs in a multidisciplinary weight loss clinic. Patients were assigned appointments to physician groups that selected AOM treatments based on phenotype or to physicians who recommended AOMs based on their own and/or patient preferences or related comorbidities; the latter approach was defined as standard of care for AOM selection (1,8,9). Thus, this design constituted a pragmatic, real-world study. The Consolidated Standards of Reporting Trials (CONSORT) flow of participation and allocation of treatment appears in Supporting Information Figure S1. See the CONSORT-extension guidelines checklist in Supporting Information (36).

The multidisciplinary program in the Obesity Clinic involves a team of providers, registered dietitians, and behavioral psychologists. The detailed description of the weight management program is provided in online Supporting Information. Participants in the phenotype-guided group had their phenotype measured by clinically available tests (satiation test [nutrient drink test]; satiety test [gastric emptying by scintigraphy]; emotional hunger [validated questionnaires]; and energy

TABLE 1 Summary of key energy balance variables studied, intermediary end point, and results based on first 100 patients who completed all the phenotyping tests

| Obesity category | Phenotype | Test | Results | | |
|----------------------------|-------------------------------|--|---------------------|---------------------|----------------------|
| | | | All cohort | Females | Males |
| Food intake—homeostatic | Satiation (hungry brain) | Ad libitum buffet meal, kcal | 803 (660-1,054) | 762 (631-894) | 1,104 (802-1,376) |
| | | VAS—Satisfaction 30 min postprandial, 0-100 mm | 97 (93-100) | 98 (94-100) | 95 (90-100) |
| | Satiety (hungry gut) | VAS—Fullness 120 min postprandial, 0-100 mm | 64 (44-82) | 63 (42-83) | 66 (49-80) |
| | | Gastric emptying $T_{1/2}$, min | 118 (99-139) | 123 (101-142) | 99 (86-113) |
| Food intake—hedonic eating | Emotional eating | TEFQ—Emotional Restraint (4-16 scale) | 7 (4-13) | 7 (4-13) | 7 (4-12) |
| | | HADS-A (0-21 scale) | 4 (2-7) | 4 (2-7) | 4 (2-7) |
| Energy expenditure | Basal metabolic rate | Predicted REE (HB) % | 101 (95-108) | 102 (96-110) | 97 (94-103) |
| | Nonexercise physical activity | Self-reported steps, # | 3,375 (3,000-9,000) | 3,000 (3,000-8,500) | 5,350 (3,000-10,000) |
| | Exercise | Self-reported exercise (PASC), 0-8 scale | 6 (5-7) | 5 (5-7) | 6 (5-8) |

The demographics of this cohort were median (IQR): age 38 (30-44) years, BMI 36 (33-42) kg/m², and 73% females. Data shown in median (IQR).

HADS-A, Hospital Anxiety and Depression Score-Anxiety; HB, Harris-Benedict equation; IQR, interquartile range; PASC, Physical activity stage of change assessment tool; REE, resting energy expenditure; TEFQ, Three Factor Eating Questionnaire; VAS, visual analog scale.

expenditure [indirect calorimetry REE]). Participants in the nonphenotyped group had no test prior to medication selection.

Rationale for a priori phenotype-guided AOM approach. Treatment decisions in the phenotype-guided group were determined by an a priori management approach based on the medications' predominant mechanism of action (9) and supported by previously completed randomized, placebo-control trials (26,37,38). Those prior trials showed that a phenotype-tailored application may predict best responders for the following medications: phentermine-topiramate extended release for the hungry brain phenotype (26) and exenatide and liraglutide for the hungry gut phenotype (37,38). Lorcaserin was selected for the hungry brain phenotype as the predominant mechanism of action is to induce satiation by activating (5-HT)_{2C} receptors in the hypothalamus (9). Naltrexone/bupropion sustained release was selected for the emotional hunger phenotype as bupropion is a dopamine/norepinephrine reuptake inhibitor and naltrexone is an opioid receptor agonist; together they modulate appetite, mood, and cravings (9). Phentermine was selected for the slow burn phenotype for its secondary effect on energy expenditure (9).

Based on the obesity phenotype classification, AOMs were selected as follows:

1. abnormal satiation ("hungry brain"): phentermine-topiramate extended release (Qsymia, Campbell, California) at a dose of 7.5/46 mg daily or lorcaserin (Belviq, Arena Pharmaceuticals, San Diego, California) at 20 mg daily (patients were told to discontinue in February 2020 based on U.S. Food and Drug Administration [FDA] recall);
2. abnormal hedonic eating ("emotional hunger"): oral naltrexone/bupropion sustained release (Contrave, Nalpropion Pharmaceuticals, Morristown, New Jersey) at a dose of 16/180 mg twice daily;
3. abnormal satiety ("hungry gut"): liraglutide (Saxenda, Novo Nordisk, Plainsboro, New Jersey) 3 mg subcutaneous daily; or
4. low predicted energy expenditure ("slow burn"): phentermine 15 mg daily plus increased resistance training.

When patients had two or more phenotypes, the providers selected the medication based on the predominant phenotype. Patients were excluded if no phenotype was identified, when patients had contraindications, or if there was a lack of insurance coverage for the "assigned" medication.

Design of clinical trial and eligibility criteria. We report the outcomes of 84 patients who received phenotype-guided treatment compared with 228 patients who received standard of care weight loss treatment with medications not based on phenotype characterization.

Participants included in the analysis met these inclusion criteria: (1) patients with BMI ≥ 27 kg/m² with adiposity-related comorbidities or patients with BMI ≥ 30 kg/m² with or without adiposity-related comorbidities; (2) patients prescribed FDA-approved AOMs; (3) follow-up of at least 3 months; and (4) two or more face-to-face visits with one of the physicians at the Mayo Clinic Weight Management Program.

We excluded all patients who (1) had prior major gastrointestinal surgery, (2) had prior endoscopic weight loss intervention, (3) did not fill the medication prescription because of health insurance coverage denial and/or high drug cost, and (4) were taking FDA-approved AOMs prior to the first visit to the Mayo Clinic Weight Management Program, because such a prior prescription may conceivably confound the weight

loss outcomes. All the information was collected from physician's documentation, including outcomes and adverse events.

End points and statistical analysis

In the pragmatic trial, the primary end point was the percentage of total body weight loss (TBWL) during 1-year follow-up. Secondary end points included the proportion of patients who had a reduction from baseline body weight of $\geq 5\%$, $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$. See online Supporting Information materials and protocol for details.

All continuous data are summarized as means and SEMs or group mean differences with 95% confidence intervals unless otherwise stated. Categorical data are presented as frequencies and percentages. We used unpaired two-tailed *t* test for between-group comparisons for baseline nominal and ordinal variables and χ^2 for categorical variables. Additional details of sample size, primary and secondary end points, and detailed statistical analysis are provided in the Methods section of the online Supporting Information. *P* < 0.05 was considered statistically significant.

Results

Obesity phenotypes classification

We studied a total of 450 participants with obesity (defined as BMI > 30 kg/m²) with the following demographics (mean [SEM]): age 39 (0.5) years old, BMI 37 (0.3) kg/m², 72% females, 93% White, waist circumference 105 (0.1) cm, and fasting glucose 103 (1.4) mg/dL (Table 2). We classified obesity in four distinct phenotypes: hungry brain (abnormal satiation), emotional hunger (hedonic eating), hungry gut (abnormal satiety), slow burn (decreased metabolic rate), and no phenotype. The phenotype distribution and overlap are shown in Figure 1B.

The prevalence of each phenotype was hungry brain 32% (*n* = 143/450), emotional hunger 21% (*n* = 96/450), hungry gut 32% (*n* = 144/450), slow burn 21% (*n* = 82/400), and no identified phenotype 15% (*n* = 68/450). Two or more phenotypes were documented in 27% of patients (mixed group). The prevalence of participants with only one phenotype was hungry brain 16%, emotional hunger 12%, hungry gut 18%, and slow burn 12% (Figure 1B). Among these phenotype groups, there were statistical differences in gender (ANOVA *P* < 0.01) and race (ANOVA *P* < 0.01), with the percentage of males being higher in the hungry gut and slow burn phenotypes and the percentage of White race being lower in the hungry gut compared with the other groups. There was no statistical difference in age, height, body weight, BMI, waist or hip circumference, pulse, blood pressure, fasting glucose, and prevalence of comorbidities (Table 2).

Based on the selected cutoffs in each phenotype, the differences in each phenotype compared with participants without that specific phenotype were as follows: the hungry brain group consumed 62% more calories prior to reaching fullness; the emotional hunger group reported 2.8 times higher levels of anxiety; the hungry gut group emptied the stomach contents 31% faster; and the slow burn group had 12% lower predicted REE when compared with the other groups of obesity (Table 2 and Figures 2A-2D).

Individuals with the emotional hunger obesity phenotype had higher levels of symptoms of anxiety (*P* < 0.001), symptoms of depression (*P* < 0.001), emotional restraint-TEFQ21 (30% higher, *P* = 0.04), and emotional eating (Disinhibition on the Eating Inventory, *P* = 0.007)

TABLE 2 Participant characteristics including demographics, anthropometric measurements, and comorbidities in all the cohorts and per obesity phenotype (showing the demographics in abnormal phenotype compared with normal phenotype)

| | Phenotype | | | | | | ANOVA <i>P</i> |
|------------------------------|------------|-----------------|---------------|------------------|---------------|--------------|--------------------|
| | All cohort | Hungry brain | Hungry gut | Emotional hunger | Slow burn | None | |
| <i>Demographics</i> | | | | | | | |
| Prevalence, <i>n</i> (%) | 450 (100%) | 143/450 (32%) | 144/450 (32%) | 96/450 (21%) | 82/400 (21%) | 68/450 (15%) | |
| Age, y | 39±0.5 | 37±0.9 | 39±0.9 | 37±1.2 | 39±1.2 | 40±1.3 | 0.19 |
| Gender (F), % | 72 | 78 | 67 | 75 | 57 | 83 | 0.009 [#] |
| Race (White), % | 93 | 96 | 89 | 96 | 95 | 100 | 0.01 [#] |
| Weight, kg | 107±1.0 | 108±1.7 | 106±1.7 | 111±2.2 | 115±3.2 | 106±2.4 | 0.09 |
| Height, cm | 169±0.4 | 170±0.8 | 169±0.8 | 169±0.9 | 171±1.1 | 168±1.0 | 0.16 |
| BMI, kg/m ² | 37±0.3 | 37±0.5 | 36±0.5 | 39±0.7 | 39±0.8 | 38±0.8 | 0.07 |
| Waist, cm | 105±0.1 | 106±1.3 | 107±1.1 | 108±2.0 | 104±2.3 | 105±1.1 | 0.82 |
| Hip, cm | 120±0.1 | 121±1.1 | 121±1.0 | 122±1.9 | 117±1.4 | 120±1.3 | 0.80 |
| Pulse, beats/min | 74±0.6 | 74±1.0 | 73±0.9 | 74±1.3 | 75±1.5 | 77±2.0 | 0.25 |
| SBP, mmHg | 131±0.7 | 132±1.3 | 133±1.3 | 130±1.4 | 131±2.0 | 131±2.1 | 0.15 |
| DBP, mmHg | 82±0.6 | 80±0.9 | 81±1.0 | 79±1.1 | 81±1.4 | 83±1.4 | 0.45 |
| Fasting glucose, mg/dL | 103±1.4 | 101±2.8 | 103±1.5 | 98±1.8 | 97±2.2 | 102±1.9 | 0.55 |
| Comorbidities [^] | 1.1±0.1 | 1.1±0.1 | 1.0±0.2 | 1.3±0.3 | 1.3±0.1 | 0.9±0.4 | 0.19 |
| <i>Phenotyping tests</i> | | | | | | | |
| Ad libitum buffet meal, kcal | 929±16 | 1,224±25 | 996±26 | 990±34 | 918±35 | 700±21 | <0.001 |
| Gastric emptying T½, min | 110±1.4 | 107±2.2 | 83±1.4 | 111±2.7 | 117±3.3 | 133±3.4 | <0.001 |
| HADS-Anxiety (0-21 scale) | 4±0.1 | 4±0.3 | 3.7±0.2 | 8.1±0.2 | 3.9±0.1 | 2.4±0.2 | <0.001 |
| Predicted REE (HB), % | 100±0.6 | 102±1.4 | 100±1.4 | 103±1.1 | 89±0.6 | 106±0.8 | <0.001 |

Bold numbering represents the phenotype matched with its respective phenotype test. Data shown as mean ± SEM.

[#]Pearson test.

[^]Obesity-related comorbidities: type 2 diabetes, gastroesophageal reflux disease, high blood pressure, hyperlipidemia, obstructive sleep apnea, degenerative joint disease, asthma, other).

HADS-A, Hospital Anxiety and Depression Score-Anxiety; REE, resting energy expenditure; HB, Harris-Benedict equation.

and lower levels of self-esteem ($P=0.002$) and body image ($P<0.001$) compared with non-emotional-eating obesity phenotypes.

In female participants with hungry gut obesity, the mean gastric emptying $T_{1/2}$ was accelerated by 30% for solids ($P<0.001$) and by 22% for liquids ($P=0.01$) compared with non-hungry-gut obesity among females. In male participants with hungry gut obesity, mean gastric emptying $T_{1/2}$ was accelerated by 38% for solids ($P<0.001$) and 33% for liquids ($P=0.05$) compared with non-hungry-gut obesity among males.

Participants with slow burn obesity had a lower muscle mass (non-slow burn obesity phenotype $50.7\% \pm 0.6\%$, compared with slow burn obesity phenotype $46.7\% \pm 0.7\%$, $P<0.001$), reported to be less frequently active ($P=0.048$), less engaged in structured exercise ($P=0.05$), and among those who engaged in structured exercise, they performed exercise for fewer minutes ($P=0.04$) compared with participants with non-slow burn obesity.

Pragmatic trial of phenotype-guided compared with standard of care selection of AOMs

Participant characteristics. There were statistical differences in the demographics and comorbidities among the groups. Patients in the phenotype-guided group were younger (mean difference 7.2 years [95% CI -4 to -10.4], $P<0.001$) and had lower systolic blood pressure

(SBP) (mean difference 6.2 mmHg [95% CI -11 to -1.5], $P=0.01$) and lower fasting glucose (mean difference 21 mg/dL [95% CI -37 to -3.2], $P=0.02$) compared with the nonphenotyped (standard of care use of medications) group (Table 3). There were no statistically significant differences in gender, race, anthropometric measurements, diastolic blood pressure (DBP), hemoglobin A1c (HbA1c), number of comorbidities, average length of follow-up, or number of visits with providers, psychologists, and registered dietitians between the phenotype-guided group compared with the non-phenotype-guided group (Table 3). Importantly, there was no statistically significant difference in the prevalence of type 2 diabetes (phenotype-guided group, 25% compared with the non-phenotype-guided group, 29%, $P=0.41$). In patients with a prior diagnosis of diabetes, the HbA1c was lower in the phenotype-guided group compared with the non-phenotype-guided group (mean difference 1.2% [95% CI -2 to -0.3], $P=0.02$). There was no difference in fasting glucose or number of diabetes medications used among the groups (Supporting Information Table S1).

In the phenotype-guided group, the prevalence of participants' phenotypes was hungry brain (40%), emotional hunger (30%), hungry gut (18%), and slow burn (12%), and medications were selected for each phenotype as described in the methods. In the nonphenotyped group, medications were selected based on AOM side effect profile (30%), glycemic control (21%), patient preference (16.5%), cravings (10%),

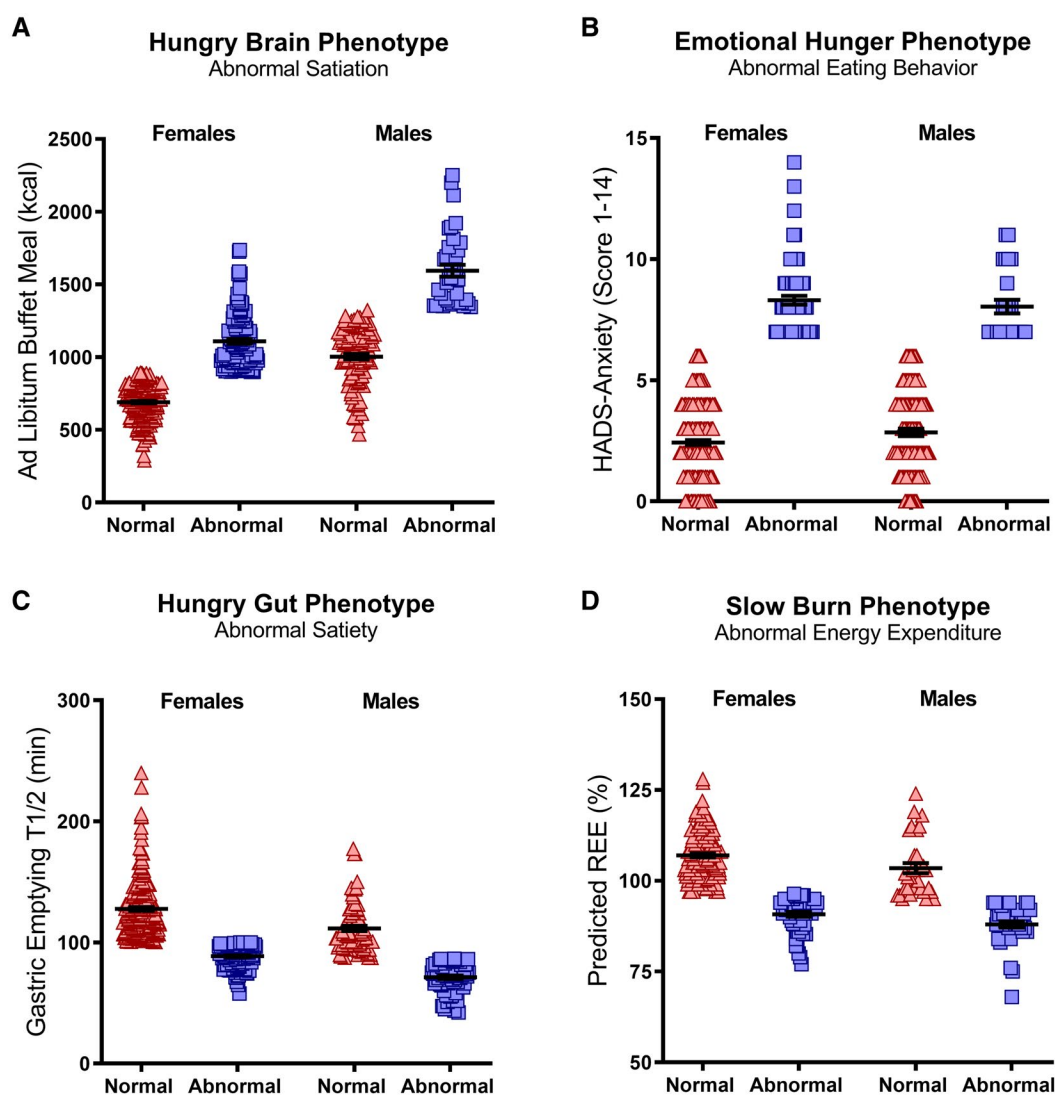


Figure 2 Obesity phenotype characteristics per gender. Obesity phenotypes are associated with pathophysiological characteristics; (A) hungry brain, increased food intake until fullness during ad libitum buffet meal; (B) emotional hunger; increased HADS-anxiety level; (C) hungry gut, rapid gastric emptying rate; (D) slow burn, lower than predicted REE. Red triangles=participants without specified obesity phenotype, blue squares=participants with specified obesity phenotype. HADS, Hospital Anxiety and Depression Score; REE, resting energy expenditure.

insurance preference (10%), previous successful attempts with same medication (6.5%), abnormal satiety (1%), and other/unknown reason (5%). Metformin was prescribed, as an adjunct weight loss medication, in 10% of the phenotyped group and in 26.8% of the nonphenotyped group ($P=0.015$). There was a significant difference in the proportion of AOMs used in each group (Table 3, $P<0.001$). There was no statistical difference in the most common prescribed dose for naltrexone-bupropion sustained release (16–180 mg twice daily), lorcaserin (10 mg daily), and phentermine-topiramate ER (7.5–46 mg daily). The proportion of patients who received phentermine 37.5-mg prescription was numerically different with 0% in the phenotyped group compared with 29% of the nonphenotyped group ($P=0.07$). Liraglutide 1.8-mg dose was less commonly used in the phenotyped group (43%) compared with the nonphenotyped group (79%, $P=0.02$).

Comparison of efficacy of two treatment strategies. Mean weight loss (SEM) at 6 months of treatment, with more than 93% retention in both groups, was -10.5% (0.8%) in the phenotype-guided group and -6.3% (0.4%) in the non-phenotype-guided group (mean difference -4.1% [95% CI -5.9% to -2.5%], $P<0.001$). At 12 months, mean weight loss was -15.9% (1.1%) in the phenotype-guided group compared with -9.0% (0.6%) in the non-phenotype-guided group (mean difference -6.9% [95% CI -9.4% to -4.5%], $P<0.001$) (Figure 3B, Table 3). Using the last observation carried forward, mean weight loss was -12.1% (0.9%) in the phenotype-guided group compared with -7.8% (0.5%) in the non-phenotype-guided group (mean difference -4.3% [95% CI -6.2% to -2.3%], $P<0.001$). Phenotype-guided obesity pharmacotherapy resulted in 79%, 43%, and 30% of patients achieving clinically significant absolute weight loss of $>10\%$, $>15\%$,

TABLE 3 Participant characteristics and outcomes of antiobesity pharmacotherapy in a phenotype-guided intervention vs. non-phenotype-guided intervention (standard of care)

| Characteristic | Variable | Phenotype-guided therapy | Non-phenotype-guided therapy | Difference (95% CI) | P |
|-----------------------|-----------------------------------|--------------------------|------------------------------|---------------------|------------------|
| Patient demographics | <i>N</i> | 84 | 228 | | |
| | Age, y | 43±1.4 | 50±0.9 | 7.2 (−4 to −10.4) | <0.001 |
| | Gender (F), % | 74 | 73 | | 0.26 |
| | Race (White), % | 94 | 98 | | 0.10 |
| | Weight (kg) | 121±2.6 | 118±1.8 | 3.3 (−2.8 to 9.4) | 0.28 |
| | Height (cm) | 169±0.9 | 168±0.6 | 0.9 (−1.3 to 3) | 0.42 |
| | BMI, kg/m ² | 42±0.7 | 41±0.5 | 0.69 (−1.1 to 2.5) | 0.44 |
| | Blood pressure (SBP), mmHg | 124±2.1 | 130±1.1 | 6.2 (−11 to −1.5) | 0.01 |
| | Blood pressure (DBP), mmHg | 79.4±1.4 | 79±0.8 | 0.6 (−2.7 to 3.9) | 0.71 |
| | Fasting glucose, mg/dL | 106±6 | 127±7 | 21 (−37 to −3.2) | 0.02 |
| | Hemoglobin A1c, % | 6.3±0.3 | 7±0.2 | 0.7 (−1.5 to 0.1) | 0.10 |
| | Comorbidities, <i>n</i> | 2±0.2 | 2.4±0.1 | 0.37 (−0.8 to 0.02) | 0.06 |
| Medication use | Naltrexone-bupropion SR | 24 (29%) | 17 (8%) | | <0.001 |
| | Liraglutide | 13 (16%) | 48 (21%) | | |
| | Lorcaserin | 10 (12%) | 8 (4%) | | |
| | Phentermine | 11 (13%) | 39 (17%) | | |
| | Phentermine-topiramate ER | 26 (30%) | 116 (50%) | | |
| Intervention | Follow-up, mo | 8.2±0.5 | 8.1±0.3 | 0.17 (−1 to 1.4) | 0.78 |
| | No. follow-up visits | 3.3±0.1 | 3.1±0.1 | 0.2 (−0.3 to 0.4) | 0.38 |
| | Pts with >1 follow-up visit | 78 (93%) | 206 (93%) | | 0.97 |
| | with physician in 0-6 months | | | | |
| | Pts with ≥1 follow-up visit | 50 (59.4%) | 122 (54%) | | 0.29 |
| | with physician in 6-12 months | | | | |
| | Pts with >1 dietitian visit | 24 (29%) | 82 (37%) | | 0.37 |
| | No. dietitian visits | 0.78±0.2 | 0.66±0.1 | 0.12 (−0.2 to 0.5) | 0.45 |
| | Pts with >1 psychiatric visit | 19 (23%) | 74 (33%) | | 0.32 |
| Intervention outcomes | No. behavioral psychiatric visits | 0.56±0.3 | 1.2±0.2 | −0.6 (−1.2 to 0.02) | 0.06 |
| | Weight loss at 3 months, % | −5.4±0.5 | −5.1±0.3 | −0.3 (−1.4 to 0.8) | 0.61 |
| | Weight loss at 6 months, % | −10.5±0.8 | −6.3±0.4 | −4.1 (−5.9 to −2.5) | <0.001 |
| | Weight loss at 12 months, % | −15.9±1.1 | −9±0.6 | −6.9 (−9.4 to −4.5) | <0.001 |
| Adverse events | Weight loss at LOCF, % | −12.1±0.9 | −7.8±0.5 | −4.3 (−6.2 to −2.3) | <0.001 |
| | Documented adverse events | 11 (14%) | 46 (20%) | | 0.23 |

Data shown as mean ± SEM. Bolding denotes statistical significance ($P < 0.05$).

LOCF, last observation carried forward; ER, extended release; SR, sustained release

and >20%, respectively, at 1 year compared with 35%, 17%, and 8% of patients in the nonphenotype approach (Figure 3A, $P < 0.001$). The failure rate (defined as less than 5% TBWL) was 2% in the phenotype-guided group compared with 26% in the non-phenotype-guided group ($P < 0.001$).

Individual weight loss in the whole cohort and per medication is reported in Supporting Information Figure S2. The weight loss for each medication at 12 months in the phenotype-guided group compared with the non-phenotype-guided group was statistically significant for phentermine-topiramate extended release, lorcaserin, and liraglutide; there was a positive trend for bupropion-naltrexone sustained release ($P = 0.07$) (Supporting Information Figure S3). There was no statistical

difference in early response rate (proportion of patients with >5% TBWL at 3 months) in the phenotyped group (56.1%) compared with the non-phenotyped group (51.8%). For the early responders, the weight loss at 12 months was −18.3% (1.6%) TBWL in the phenotype-guided group compared with 13.98% (1.1%) in the non-phenotype-guided group ($P = 0.03$).

In patients with diabetes, the mean weight loss at 6 months of treatment was −9.7% (1.4%) in the phenotype-guided group and −5.3% (0.7%) in the non-phenotype-guided group (mean difference −4.4% [95% CI −7.7 to −1.1], $P = 0.01$) and at 12 months was −12% (1.7%) in the phenotype-guided group compared with −6.3% (1%) in the non-phenotype-guided group (mean difference −5.7% [95% CI −9.8 to −1.5], $P = 0.009$) (Supporting Information Table S1).

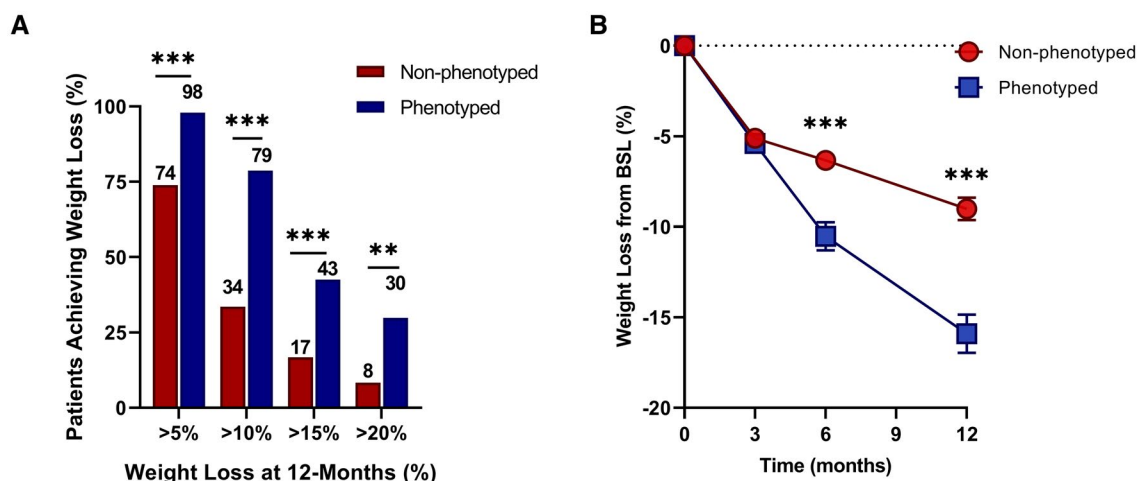


Figure 3 PG pharmacotherapy for obesity management improves weight loss outcomes. (A) Percentage of patients achieving levels of weight loss after 1 year of either non-PG ($n=228$) or PG ($n=84$) treatment. (B) The average percentage of total body weight loss from BSL in non-PG (red circles) and PG (blue squares) treatment at 3, 6, and 12 months. $^{**}P<0.01$, $^{***}P<0.001$. BSL, baseline; PG, phenotype guided.

When adjusted for age, gender, HbA1c, and SBP, the mean weight loss difference at 12 months was -13.6% (2.2%) in the phenotype-guided group compared with -6.6% (1.1%) in the nonphenotyped group (mean difference -6.97 [95% CI -12.1 to -1.9], $P=0.009$). Baseline phenotype and HbA1c were the only significant covariates.

Adverse events. There were no significant differences in AOM-induced adverse events among the groups. There was a numerically lower incidence of adverse events to phentermine and liraglutide in the phenotyped group (14%) compared with the nonphenotyped group (30%).

Discussion

Our study of participants with obesity has shown clinically meaningful phenotype-based groups identified by validated biological and behavioral testing of the key components of energy balance. This phenotype-based classification reduces the heterogeneity of obesity and facilitates further understanding of the pathophysiology within each phenotype. Phenotype-guided obesity pharmacotherapy enhanced weight loss in a precision medicine, pragmatic trial.

Despite considerable attempts to address the obesity heterogeneity and predictors for weight loss in the literature, there are no established predictors of response to obesity interventions (3,16). The phenotype-based classification proposed addresses, at least in part, the underlying pathophysiology of energy balance and considers gender as the initial key variable in obesity phenotype stratification. We identify within four obesity-related phenotypes the associated pathophysiological perturbations that underpin, at least in part, the phenotype as summarized here: (a) “hungry brain,” characterized by excessive calories consumed to terminate meal; (b) “emotional hunger,” characterized by negative mood, emotional eating, cravings, and reward-seeking behaviors, despite having normal homeostatic eating behavior (39); (c) “hungry gut,” characterized by reduced duration of fullness, quantified objectively by rapid gastric

emptying; and (d) “slow burn,” characterized by reduced REE, reduced reported physical activity and exercise, and with lower muscle mass.

Fifteen percent of participants did not meet the criteria for any single phenotype, which suggests that more variables must be studied to fully understand the complexity of obesity in a minority of patients. Furthermore, the fact that 27% of participants have two or more phenotypes of obesity illustrates this complexity, which may indicate that some patients with obesity might need combination therapy to treat the underlying aberrant mechanisms (40).

The utility of the phenotype-based classification of obesity is supported by the observed responses to phenotype-guided weight loss therapy. Currently, FDA-approved AOMs are usually prescribed based on physician and patient preferences, related comorbidities, insurance coverage, or potential risk profile (1,8,9). Here, we propose a new treatment approach whereby phenotypes guide AOM selection, based on and in accordance with the mechanism of action (9). This is supported by prior experience from three prior single-center, randomized, double-blinded, placebo-controlled clinical trials that identified best responders according to the phenotypes of increased food intake and accelerated gastric emptying (24,35,37). Thus, the proposed phenotype-guided approach consists of using the FDA-approved AOMs based on potential mechanism of action in relation to the phenotype(s): phentermine-topiramate extended release for hungry brain, bupropion-naltrexone sustained release for emotional hunger, liraglutide for hungry gut, and low-dose phentermine plus resistance training for the slow burn phenotype. In the current pragmatic clinical trial, with this a priori-defined approach, we observed that phenotype-guided pharmacotherapy more than doubled the responder rate when adjusted for age, gender, SBP, and HbA1c and increased the total weight loss by an average 75% compared with standard care, which also used the AOMs without consideration of the phenotype.

These outcomes require replication and validation in larger, more racially and metabolically diverse cohorts, preferably in multicenter,

randomized studies. However, the real-world, pragmatic trial design may be perceived as a strength of the study, which may accelerate the applicability of the research findings to patient management and AOM selection. Additional studies are needed to identify best responders for participants with two or more phenotypes or those with no phenotype, which may require a low-calorie diet challenge to trigger a metabolic adaptation or weight-loss-induced phenotype. Additional, further studies are needed to understand whether AOMs with multiple mechanisms of action may have a positive outcome in other phenotypes, for example, using bupropion-naltrexone sustained release to induce satiation (41) or liraglutide for food cravings (42). However, the benefits seen with a phenotype-guided approach over standard of care warrant the additional testing in the management of obesity. Such confirmation would be a step toward a mechanistic and evidence-based, personalized approach to obesity. Furthermore, this classification may also reduce the stigma associated with obesity (43), reduce or eliminate the trial and error (standard of care) selection for AOMs, potentially increase provider confidence and patient engagement in the treatment journey, and facilitate patient-provider discussion and individualized choice of treatment for obesity.

We perceive that other etiologies of obesity may be considered in future pathophysiological classifications, and therefore it is essential to further interrogate the roles of genetics, epigenetics, microbiome, and exposure in obesity phenotypes, and in outcomes to obesity treatments, including nonpharmacological approaches. Additionally, the outcome with phenotype-guided pharmacotherapy has limitations that deserve further studies in the future, including appraising a “testing” bias such that participants who underwent additional testing may be conditioned to greater responsiveness based on clinical education and consent, lack of blinded randomization, and potential group-difference confounders such as age and comorbidities. Despite these limitations, the weight loss difference was almost doubled when adjusting for potential confounders. It is worth noting that there was persistent weight loss observed in this pragmatic trial in both groups of patients and that there was continued weight loss with AOM treatment administered for 12 months. A prior real-world report of AOM efficacy has shown similar effects of continued weight loss at 6 months (44), which differs from larger randomized trials in which weight loss is typically seen in the first 3 months (1,5-7). However, early response seems to also determine overall weight loss over 12 months in the phenotype-guided approach to AOM treatment, as previously described in randomized trials (6,7).

In summary, we have identified actionable phenotypes of obesity based on pathophysiology and behavior that elucidate human obesity heterogeneity and that can be targeted to enhance weight loss outcomes of pharmacotherapy. This phenotype-based classification reduces the heterogeneity of obesity, and it may serve as a valuable tool to understand the pathogenesis that leads to human obesity and to accelerate the translation of discovery into phenotype-specific targeted trials. In the era of individualized medicine, the proposed phenotype-guided stratification and treatment approach, in addition to the positive outcomes reported in previous randomized trials (24,35,37), represents a step toward a mechanistic, precision medicine approach to optimize obesity therapy. **O**

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Disclosure: Phenomix Sciences has obtained an exclusive license to AA and MC's biomarker technology, submitted patent, and know-how to develop a biomarker to predict response to obesity pharmacotherapy. Additionally, AA is a stockholder in Gila Therapeutics and Phenomix Sciences; he serves as a consultant for Rhythm Pharmaceuticals and General Mills. MC is a stockholder in Phenomix Sciences and Enterin and serves as a consultant to Takeda, Allergan, Kallyope, GlaxoSmithKline, Rhythm, and Arena with compensation to Mayo Clinic. MMC is a consultant for Roche Diabetes Care GmbH. BAD has served as a consultant for Boston Scientific, Metamodix, BFKW, DyaMx, and USGI Medical; has received research support for Boston Scientific, Apollo Endosurgery, USGI, Spatz Medical, GI Dynamics, Caim Diagnostics, Aspire Bariatrics, and Medtronic; and has been a speaker for Johnson & Johnson, Endogastric Solutions, and Olympus. The other authors declared no conflict of interest.

Author contributions: AA, MC, BAD, and MMC: concept development, phenotyping, study design, data interpretation, manuscript writing/editing. GC, AM, DG, SS, WR, and DB: data collection and analysis, manuscript writing/editing. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the decision to submit for publication.

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