Early Weight Loss in Behavioral Treatment Predicts Later Rate of Weight Loss and Response to Pharmacotherapy

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Abstract

Background Early weight loss (EWL) in the first 1–2 months of behavioral treatment is a strong predictor of later total weight loss. It is not clear whether participants with lower early losses lose less in ongoing treatment or simply fail to overcome the smaller initial loss. Furthermore, no study has tested whether EWL in behavioral treatment predicts response to a different treatment modality, such as pharmacotherapy.

Methods Data were from 170 participants with obesity (baseline BMI = 40.8 ± 5.8 kg/m², 87.6% female; 71.3% Black) enrolled in a two-phase trial. Data from the weight loss phase, which provided weekly lifestyle counseling and a meal replacement diet, were used to examine the relationship between 4-week EWL and subsequent rate of weight loss in behavioral treatment. Data from the maintenance phase, in which 137 participants who had lost $\geq 5\%$ of initial weight were randomized to 52 weeks of maintenance counseling with lorcaserin or placebo, were used to determine whether EWL with behavioral treatment affects the benefit of pharmacotherapy.

Results EWL in the first 4 weeks of behavioral treatment ($3.6 \pm 1.7\%$) predicted greater total losses at Week 14 ($r^2 = 0.61$, $p < .001$) and a faster rate of weight loss in the subsequent 9 weeks of the program ($p < .001$). During the maintenance phase, lower EWL in behavioral treatment predicted a greater benefit of lorcaserin, in comparison with placebo, for the maintenance of a $\geq 5\%$ loss at Weeks 24 and 52.

Conclusions These findings support recommendations to modify treatment for individuals with low EWL.

Keywords Obesity • Early weight loss • Weight loss predictors • Behavior therapy • Anti-obesity agents

Introduction

Early weight loss (EWL) in the first 1–2 months of behavioral treatment for obesity is a strong predictor of a patient's total weight loss and likelihood of achieving a clinically meaningful loss $\geq 5\%$ of initial weight at the end of treatment and up to 8 years later [1–6]. Several researchers have, thus, recommended that patients with low EWL be provided with a different or supplemental treatment as early as possible, rather than spending 6 months or more in a program that is unlikely to induce a clinically significant loss [1–4].

Surprisingly little is known about the mechanisms through which EWL influences long-term weight loss. Patients with relatively low EWL, who lost at a slower rate than their peers during the first 1–2 months, could continue to lose at a slower rate as behavioral treatment continues. The difference in weight loss between patients with low and high starting rates would grow larger over time. Alternatively, patients with low and high EWL could have similar rates of weight loss after the first 1–2 months. Those with lower EWL would still end treatment with smaller losses, unable to compensate for their slower start. In this latter case, rather than introducing

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a new treatment for those with low EWL, these patients might benefit from increasing the number or duration of early treatment visits, given that they catch on to treatment as they complete more weeks of intervention.

Expert guidelines recommend weight loss medications as an adjunct to behavioral treatment in patients who do not achieve clinically meaningful weight losses with behavioral intervention alone [7]. Pharmacotherapy and behavior therapy have been shown to produce additive weight loss in randomized controlled trials [8]. However, if patients with lower weight loss in behavioral treatment also lose relatively less weight with pharmacotherapy, the benefit of this added intervention would be small. To our knowledge, no study has examined whether EWL in behavioral treatment is related response to obesity pharmacotherapy.

The present study had two primary aims: (i) to determine whether EWL in the first 4 weeks of behavioral treatment would predict rate of weight loss in ongoing treatment (e.g., after Week 5) and (ii) to determine whether EWL with behavioral treatment would predict weight change when pharmacotherapy was subsequently introduced. We examined these relationships using data from a two-phase trial [9] in which all participants completed an initial 14-week, group lifestyle intervention that included the use of a meal-replacement diet (i.e., Phase 1). Participants who lost $\geq 5\%$ of their initial weight were then eligible to participate in a 52-week double-blind randomized controlled trial (RCT) comparing the efficacy of lorcaserin, a selective serotonin 2C receptor agonist approved in 2012 for chronic weight management, to placebo for weight loss maintenance (i.e., Phase 2). Lorcaserin is thought to improve weight loss by reducing food consumption and increasing satiety [10]. Using data from Phase 1, we first tested whether 4-week EWL was associated with total weight loss and success in losing $\geq 5\%$ of initial weight at the end of the behavioral program (14 weeks). We then examined the relationship between EWL and the subsequent rate of weight loss during Weeks 5–14 of the program. Data from Phase 2 were used to examine whether EWL in behavioral treatment was associated with a greater benefit of lorcaserin, as compared with placebo, for the maintenance of lost weight during the RCT.

Methods

Participants

Participants were recruited from local media advertisements and completed a telephone prescreening and an in-person behavioral and medical screening [9]. A total of 178 participants enrolled in the Phase 1 lifestyle modification program, of whom 137 (77.0%) were randomized to lorcaserin or placebo in Phase 2, the weight loss maintenance RCT. (A total of 150 participants [84.2%] completed Phase 1, of whom seven did not achieve a weight

loss $\geq 5\%$ and six were lost to follow-up or excluded). The study's design, methods, and inclusion criteria have been described in detail elsewhere [9]. Briefly, participants were aged 21–65 years, had a body mass index (BMI) $\geq 33 \text{ kg/m}^2$ and $\leq 55 \text{ kg/m}^2$ (or $\geq 30 \text{ kg/m}^2$ with an obesity-related comorbidity), and had no serious medical or psychological conditions (e.g., diabetes mellitus, recent cardiovascular disease, current major depressive disorder) or contraindications to the use of lorcaserin (e.g., pregnancy). All participants provided written informed consent, and study procedures were approved by the university's institutional review board.

Interventions

Phase 1: Weight loss induction with lifestyle modification

Phase 1 consisted of 14 weekly, 90-min group lifestyle modification sessions, delivered by registered dietitians or psychologists. Treatment materials were based on prior studies [11] and included behavioral strategies such as self-monitoring of weight and calorie intake, stimulus control, behavior analysis, goal setting, problem-solving, cognitive restructuring, and relapse prevention. Participants were prescribed a 1,000–1,200 kcal meal-replacement diet including four liquid shake servings (Health Management Resources–HMR; 160 kcal/shake), a prepackaged entrée (250–300 kcal), 1–2 servings of fruit, and a salad. The use of shakes was terminated gradually by Week 14. Participants were instructed to gradually increase their physical activity to 175 minutes/week.

Phase 2: Weight loss maintenance with lifestyle modification and pharmacotherapy

Participants who lost $\geq 5\%$ of initial weight in Phase 1 and enrolled in Phase 2 were randomized to lorcaserin (10 mg BID) or placebo and received weight loss maintenance sessions for an additional 52 weeks. Group sessions were provided every other week for the first 12 weeks (i.e., 6 sessions) and once every 4 weeks for the remainder of the 52 weeks (i.e., 10 sessions). Approximately every other session was delivered via group conference call. Session topics included the behavioral principles described above, as well as nutrition recommendations and weight loss maintenance strategies. All participants were prescribed a calorie goal of 1,200–1,800 kcal/day based on initial body weight. Participants were instructed to continue to monitor their food intake and weight and to increase their physical activity to 225 minutes/week by Week 40.

Measurement of Body Weight and Calculation of EWL

Body weight was measured at all clinic visits and at four outcome assessments (i.e., Phase 1 screening and Weeks 0 [randomization], 24, and 52 of Phase 2) using

a digital scale (Tanita BWB-800). EWL was calculated as the percent weight change from Week 1 to Week 5 of Phase 1 (i.e., 4 weeks of behavioral treatment). We chose to evaluate 4-week weight loss because this time point was most commonly used in previous studies of EWL in behavioral treatment [1–4, 6]. For seven participants who did not attend a Week 5 visit, the average of weights provided at Weeks 4 and 6 was used to compute EWL [1–4, 6]. Eight participants stopped attending treatment before Week 3 of Phase 1 and were not included in the present analyses.

Statistical Analyses

All analyses were conducted using percent weight loss as the outcome after controlling for participants' heights. We first replicated results from previous studies [1–6] by using linear regression to assess the relationship between 4-week EWL and total weight loss in Phase 1 (i.e., from the start of Phase 1) and logistic regression to assess whether EWL predicted the likelihood of achieving a loss $\geq 5\%$ of initial weight. In these analyses, total weight loss was calculated by carrying forward the last observed treatment weight. We then used linear mixed models with residual maximum likelihood to determine the relationship between 4-week EWL and the subsequent rate of weight change from Week 5 to 14 of Phase 1. Unconditional models were used to determine the appropriate model shape (e.g., linear, quadratic) and variance-covariance structure based on model fit criteria [12]. Estimates of weight change at one SD above and below the mean EWL were calculated using least squared means.

We then used linear regression and logistic regression to examine whether differences between lorcaserin and placebo in Phase 2 weight loss from randomization, total weight loss, and likelihood of maintaining the $\geq 5\%$ loss depended on level of Phase 1 EWL. In the original weight loss maintenance RCT [13], lorcaserin significantly improved weight outcomes at Week 24 but not at Week 52. We therefore examined the relationship between EWL and response to medication at both time points, with a focus on the Week 24 outcomes (when the drug had its strongest effect).

Results

Phase 1 participants who completed at least 3 weeks of treatment ($N = 170$) had a mean ($\pm SD$) initial BMI of $40.8 \pm 5.8 \text{ kg/m}^2$ ($114.2 \pm 21.0 \text{ kg}$). Their mean age was 44.5 ± 11.1 years, and they had completed 14.7 ± 2.0 years of school; 87.6% were female and 71.3% were Black (21.8% White). Participants' mean Phase 1 EWL was 3.6% of initial body weight ($SD = 1.7$, range $+0.4\%$ to -7.6%). Only 17.1% of the sample ($n = 29$)

failed to lose at least 2% of initial weight during the first 4 weeks of treatment (a commonly used criterion to define poor EWL) [3–5]. Baseline characteristics of the 137 participants who were later randomized in Phase 2 were similar to the full sample ([13], $EWL = 4.1 \pm 1.6\%$).

Effect of EWL on Weight Loss with Behavioral Treatment ($N = 170$)

EWL predicted 61.3% of the variance in total Phase 1 weight loss (i.e., from Week 1 to 14; $b = 1.74$, $SE_b = 0.10$, $p < .001$). EWL was also a significant predictor of achieving a $\geq 5\%$ loss at the end of Phase 1. Each 1% increase in EWL predicted 3.3 times greater odds of achieving a $\geq 5\%$ loss (95% CI, 2.12 to 5.19, $p < .001$).

In longitudinal analyses, 4-week EWL was a significant predictor of rate of weight change from Week 5 to Week 14 (quadratic model; $EWL \times \text{Time}$: $b = -0.11$, $SE_b = 0.02$, $p < .001$; $EWL \times \text{Time}^2$: $b = 0.003$, $SE_b = 0.001$, $p = .02$; Fig. 1). Participants with low EWL (i.e., $-1SD = -1.9\%$) lost an additional 3.2% ($SE = 0.3$) of initial weight between Weeks 5 and 14, compared with a loss of 5.9% ($SE = 0.3$, $p < .001$) in participants with high EWL (i.e., $+1SD = -5.4\%$ [Fig. 1a])

Effect of EWL in Behavioral Treatment on Response to Lorcaserin for Weight Loss Maintenance ($N = 137$)

In the original weight loss maintenance RCT [13], the lorcaserin group lost 2.4 kg ($SE = 0.8$) from randomization to Week 24, compared with a gain of 0.6 kg ($SE = 0.8$) with placebo ($p = .01$), for total losses from the start of Phase 1 of 11.7% ($SE = 0.9$) and 8.4% ($SE = 0.9$), respectively. At Week 52, the lorcaserin group had gained 2.0 kg ($SE = 0.8$) from randomization, compared with a 2.5 kg ($SE = 0.8$) gain with placebo ($p = .63$), for total losses of 7.8% ($SE = 0.8$) and 6.6% ($SE = 0.9$), respectively.

At Week 24, the difference between treatment conditions in weight change from randomization was larger at lower levels of EWL (interaction: $b = -0.69$, $SE_b = 0.31$, $p = .03$; Fig. 1b). The effect on total weight loss from the start of Phase 1 did not reach statistical significance (interaction: $b = -0.82$, $SE_b = 0.44$, $p = .06$). Participants with low EWL in Phase 1 (i.e., $-1SD = -2.5\%$) who received lorcaserin lost an additional 1.1% at Week 24, compared with a gain of 1.5% in low EWL participants who received placebo. Their total losses from the start of Phase 1 to Week 24 were 8.6% and 5.6%, respectively. Participants with high EWL in Phase 1 (i.e., $+1SD = -5.6\%$) had similar Week 24 losses with lorcaserin or placebo, both from randomization (2.1% and 1.7%, respectively) and from the start of Phase 1 (13.6% and 13.2%, respectively). EWL moderated the effect of condition on likelihood of maintaining a $\geq 5\%$ loss at Week 24 (interaction: $OR = 0.54$, 95% CI, 0.29

Fig. 1. Subsequent percentage change in body weight during (a) weight loss induction with behavioral treatment (Phase 1) and (b) weight loss maintenance with lorcaserin or placebo (Phase 2) among participants with high and low levels of EWL. (a) Phase 1 data ($N = 170$) are estimated modeled means at -1 SD (low EWL = 1.9%) and $+1$ SD (high EWL = 5.4%) in EWL. Weight loss values at Week 5 were set to 0 to highlight differences in rate of weight change after the early treatment period. Participants with high EWL lost an additional 5.9% ($SE = 0.3$) of initial body weight between Week 5 and Week 14, compared with an additional loss of 3.2% ($SE = 0.3$) among participants with low EWL. (b) Phase 2 data ($N = 137$) are estimated modeled means at -1 SD (low EWL = 2.5%) and $+1$ SD (high EWL = 5.6%) in EWL by treatment condition. Values at Phase 2 randomization were set to 0, and data labels represent weight change from randomization, such that negative values reflect additional weight loss. At Week 24, the difference between lorcaserin and placebo groups was larger at lower levels of EWL. EWL early weight loss.

to 0.98, $p = .04$). Participants with low EWL had 4.7 times greater odds of maintaining the $\geq 5\%$ loss with lorcaserin, compared with placebo (95% CI, 1.59 to 13.71, $p = .005$). Among participants with high EWL, treatment condition did not predict likelihood of maintaining the $\geq 5\%$ loss ($OR = 0.65$, 95% CI, 0.16 to 2.71, $p = .56$).

At Week 52, EWL did not moderate the effect of treatment on post-randomization (interaction: $b = -0.26$, $SE_b = 0.64$, $p = .69$) or total weight loss (interaction: $b = -0.40$, $SE_b = 0.72$, $p = .58$). However, EWL continued to predict increases in the likelihood of maintaining a $\geq 5\%$ loss with lorcaserin, compared with placebo, at lower levels of EWL (interaction: $OR = 0.34$, 95% CI, 0.30 to 0.95, $p = .03$). At Week 52, lorcaserin was associated with 4.6 times greater odds of maintaining the $\geq 5\%$ loss than placebo among participants with low EWL (95% CI, 1.38 to 14.51, $p = .01$), but it did not produce a significant advantage in participants with high EWL ($OR = 0.60$, 95% CI, 0.18 to 2.02, $p = .41$).

Discussion

In the present study, EWL in the first 4 weeks of treatment predicted over 61% of the variance in total weight loss in the 14-week behavioral program as well as greater odds of achieving a clinically meaningful loss $\geq 5\%$ of initial body weight. This study extended previous findings on the influence of EWL [1–6] by demonstrating that this link is not due to the early differences in weight change alone. EWL in the first 4 weeks of treatment predicted a faster rate of weight loss in the subsequent 9 weeks of the program, indicating that participants with larger early losses continue to lose more weight than those with slower initial losses.

In the subsequent 52-week weight loss maintenance RCT, participants with lower EWL in behavioral treatment experienced a greater benefit of lorcaserin, in comparison with placebo, for the maintenance of lost weight than those with higher initial losses. This effect was most apparent at Week 24, when the medication had its strongest effect [13]. For example, lorcaserin-treated participants with low EWL (i.e., 1 SD below the mean) had total weight losses that were 3% larger than participants treated with placebo and had 4.7 times greater odds of maintaining a $\geq 5\%$ loss at Week 24. On the other hand, lorcaserin- and placebo-treated participants with high EWL (i.e., 1 SD above the mean) had similar total losses and did not differ in their likelihood of maintaining a $\geq 5\%$ loss at Week 24. Participants with lower EWL continued to show a greater benefit of lorcaserin for the likelihood of maintaining a $\geq 5\%$ loss at Week 52.

This pattern of results generally supports the recommendation to modify an individual's treatment as soon as low EWL is identified. Participants who lose minimal weight in the initial weeks of a behavioral program are likely to continue to respond sub-optimally to ongoing treatment, but may not be at a relative disadvantage if a novel treatment method is introduced. Several studies have examined the efficacy of stepped-care approaches

in which treatment is modified for patients who do not meet EWL milestones. Typically, the initial behavioral treatments offered in these programs have been of low intensity (e.g., self-help [14, 15], Internet-based [16], or monthly visits [17]), and treatment has been intensified by increasing provider contact. Although several of these interventions have improved weight losses in early poor responders [14, 16], others have not [15, 17]. However, to our knowledge, the introduction of a categorically different intervention, such as weight loss medication, for individuals with poor EWL in behavioral treatment has not been tested in an RCT. Future studies might investigate whether individuals with poor EWL achieve a greater benefit from the introduction of a novel treatment modality than they do with intensification of the original treatment method.

The initial behavioral treatment phase in this study was short (14 weeks), and it is possible that the relationship between EWL and later rate of weight change would vary across a longer treatment period. For example, the weight change trajectories of patients with low and high early losses may become more similar over time. It would be useful for future studies to examine the relationship between EWL and rate of weight change at later time points. This research could help to identify the time period in which participants with low EWL would benefit most from a supplemental weight loss intervention.

This study had several strengths, including the analysis of the effect of EWL on later rate of weight change in addition to total change, and the use of a two-phase design to examine the impact of EWL when a different treatment is introduced. To our knowledge, this is the first study to assess whether EWL in behavioral treatment is related to response to obesity pharmacotherapy.

Several factors may limit the generalizability of these results. The study sample included a high percentage of Black women, and it is unknown whether results would generalize to other demographic groups. In addition, the average EWL was high in comparison with studies of behavioral treatments that did not provide meal replacements, and only 17.1% of the initial sample lost <2% after 4 weeks of treatment (a commonly used criterion for poor EWL), compared with 33–40% of participants in other studies [3, 4]. These larger early losses are consistent with the higher total losses seen in behavioral programs that use meal replacement products [18]; however, it is unknown whether our results would generalize to a less successful sample. Given that all participants had to complete 14 weeks of behavioral treatment and lose $\geq 5\%$ of initial weight to qualify for randomization, the individuals included in Phase 2 analyses comparing lorcaserin with placebo were, by definition, all responders to behavioral treatment. Further research is needed to

determine whether true nonresponders also can benefit from pharmacotherapy.

Although weight loss induction and maintenance with lorcaserin are related [19], we cannot determine whether EWL in behavioral treatment would predict response to lorcaserin if the medication were introduced earlier to improve initial weight losses. The introduction of lorcaserin after clinically meaningful losses had been achieved likely limited the amount of additional weight loss produced by this medication [13]. These findings can be extended by examining the benefit of medication introduced to improve weight loss induction among individuals with low EWL in behavioral treatment, as well as by assessing response to other FDA-approved medications.

In conclusion, lower EWL in a behavioral treatment program predicted a slower rate of weight loss in subsequent weeks of that treatment but was associated with a greater benefit of lorcaserin over placebo for weight loss maintenance. This study suggests that EWL is an indicator of a patient's potential to successfully lose weight with a given treatment method and supports the clinical utility of EWL to inform subsequent treatment decision making.

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Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards Jena Shaw Tronieri has received consulting fees from Novo Nordisk. Thomas A. Wadden reports receiving personal fees for serving on advisory boards for Novo Nordisk, Nutrisystem, and Weight Watchers and has received grant support on behalf of the University of Pennsylvania from Eisai Inc. and Novo Nordisk. Thomas A. Wadden and Ariana M. Chao have received grant support on behalf of the University of Pennsylvania from Shire Pharmaceuticals. Rebecca L. Pearl discloses serving as a consultant for Weight Watchers. Robert I. Berkowitz has received consulting fees from Eisai Inc. The other authors declare no conflicts of interest.

Authors' Contributions TAW was responsible for the conception and design of the parent randomized controlled trial. JST and RLP provided behavioral weight loss treatment, and RIB, NA, and AMC provided medical monitoring to patients during the randomized trial. JST organized the database, performed the statistical analysis, and wrote the first draft of the present manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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