Obesity

Effect of Obesogenic Medication on Weight- and Fitness-Change Outcomes: Evidence from the Look AHEAD Study

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Objective: This study evaluates whether obesogenic medications may decrease the effectiveness of lifestyle interventions. The authors of this study hypothesized that participants who took obesogenic medications would be less responsive to the intervention in the Look AHEAD trial.
Methods: In the trial, 5,145 participants with overweight or obesity, aged 45 to 76 years with type 2 diabetes, were randomly assigned to an intervention (vs. support and education). In this analysis, the association of exposure to obesogenic medications and successful weight loss (≥5% and ≥10% of total weight) and fitness gain (≥1 and ≥2 metabolic equivalents) was examined. For each outcome, multiple logistic regression models were fitted.
Results: Analytic sample sizes were 4,496 for weight-change analyses and 4,051 for fitness-change analyses. After adjusting for covariates, exposure to one or more obesogenic medications significantly decreased the odds of achieving ≥5% weight loss by 32% (odds ratio [OR] 0.68) and achieving ≥10% weight loss by 19% (OR 0.81). The association was dose-dependent—participants using two or more medications were less likely to achieve weight loss than those using one medication. Obesogenic medication exposure was not associated with decreased odds of achieving fitness gain overall.
Conclusions: The results suggest that exposure to obesogenic medications could hinder successful weight loss in a lifestyle intervention for people with diabetes.

Obesity (2020) **28**, 2003-2009.

Study Importance

What is already known?

- Obesogenic medication may negatively affect weight loss in behavioral weight management programs.
- Obesogenic medication may negatively affect weight loss after sleeve gastrectomy.

What does this study add?

- Obesogenic medication exposure was negatively associated with weight loss outcomes of a large lifestyle intervention trial (Look AHEAD study).

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

- More study on the association between obesogenic medication exposure and weight loss intervention outcomes is needed.
- To increase effectiveness, exposure to obesogenic medication should be taken into account when enrolling participants for a weight loss program.

Introduction

The prevalence of obesity has reached 40% among adults in the United States (1). Overweight and obesity substantially contribute to the increasing prevalence of type 2 diabetes and cardiovascular disease (CVD) (2). Furthermore, individuals with both type 2 diabetes and overweight or obesity are especially at a higher risk for CVD morbidity and mortality (3-5).

Previous studies have demonstrated that lifestyle interventions to reduce weight and increase physical activity levels resulted in ameliorating metabolic abnormalities and CVD risk factors (6-10). Therefore, the largest randomized trial of an intensive lifestyle-based weight loss intervention (Look AHEAD [Action for Health in Diabetes]) launched in 2001; the intervention aimed to reduce the risk of cardiovascular events among adults with type 2 diabetes and overweight. However, in the end, the intervention was not successful in reducing CVD event risks in this population (11). A 2016 post hoc analysis showed that participants with significant weight loss and fitness gain indeed had a lower risk of CVD events (12). However, the overall Look AHEAD trial lacked adequate efficacy because an insufficient number of participants achieved sufficient weight loss (12).

In other words, weight loss and fitness gain were effective in preventing CVD morbidity and mortality, but the weight loss program was not; this highlights the individual response variation for lifestyle

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© 2020 The Obesity Society. **Received:** 6 February 2020; **Accepted:** 15 April 2020; **Published online 5 November 2020. doi:10.1002/oby.22997**

interventions. The Look AHEAD team identified that participants with a higher level of physical activity, a lower level of caloric intake, and a higher level of self-monitoring were more likely to achieve sufficient weight loss (13).

Numerous factors could influence the efficacy of a weight loss program. However, one study has suggested that obesogenic medications might have a role (14); in more recent studies, participants exposed to obesogenic medications have shown less weight loss after a behavioral weight loss program as well as after a bariatric procedure (15,16). We hypothesize that participants taking obesogenic medications were less responsive to a randomized clinical trial intervention as well. The previous Look AHEAD analysis used weight loss and fitness gain separately for predicting CVD outcomes (12); improvement in cardiopulmonary fitness was associated with decreased CVD risk factors independent of weight loss (17,18). Nevertheless, significant weight loss could mobilize individuals to participate in different types and degrees of sports and leisure activity, paving the way for improvements in cardiopulmonary fitness (19). Obesogenic medications may interfere with fitness gain by introducing an additional barrier to sufficient weight loss. In this study, we aimed to identify the association between exposures to obesogenic medications and both weight and fitness outcomes in the Look AHEAD trial.

Methods

Description of participants and intervention

Data were obtained from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository (https://repository.niddk.nih.gov/studies/look-ahead/) for this secondary data analysis. For the Look AHEAD trial, 5,145 adults aged 45 to 76 years living with type 2 diabetes and overweight/obesity (BMI ≥ 25 kg/m^2) were recruited at 16 clinical sites in the United States from August 22, 2001, to April 30, 2004 (2,20). Participants were randomly assigned (1:1) to either an intensive lifestyle intervention (ILI) or diabetes support and education (DSE, control). Details of the intervention method are described elsewhere (2,20). Briefly, ILI participants received group and individual sessions every week for the first 6 months; for the next 6 months, they received two group sessions and one individual session per month; for years 2 to 4, they received two contacts per month. The intervention included a dietary component (aimed to reduce total calorie intake and total fat and saturated fat content), physical activity component (aimed to achieve 175 minutes of physical activity per week), and behavioral strategy component (self-monitoring, goal setting, and problem solving). DSE participants received three group sessions each year: diet, physical activity, and social support components that provided general concepts and recommendations.

Weight and height were measured in duplicate with a digital scale and stadiometer, respectively, during the baseline clinic visit and annual follow-up visits (21). For exercise capacity, a symptom-limited graded exercise treadmill test was used (22). The maximal graded exercise test was performed at baseline and submaximal exercise tests at years 1 and 4. The estimated metabolic equivalents (Mets) level was based on the speed and grade of the treadmill workload. For the maximal test, participants not taking beta-blockers had to achieve at least 85% of age-predicted maximal heart rate and a minimum of four Mets; participants taking such medicine had to achieve at least 18 on the rating of perceived exertion scale and a minimum of four Mets (21-23). For the submaximal test, participants not taking beta-blockers had to achieve at least 80% of age-predicted maximal heart rate and a minimum of four Mets; participants taking such medicine had to achieve at least 16 on the rating of perceived exertion scale and a minimum of four Mets (21-23). Outcome measures were based on the differences in weight and fitness (estimated Mets) between the baseline and year 1 clinic visits (12,24).

Exposure variables

Exposures to obesogenic medications were analyzed from three perspectives. First, the exposure variable was coded dichotomously—exposed versus not exposed to any obesogenic medications in the first year. By including obesogenic medications regardless of duration, we attempted to minimize the overinterpretation of data. Second, we examined dose-dependent relationships between exposures to obesogenic medications and outcomes—no exposure, exposed to one obesogenic medication, and exposed to two or more obesogenic medications. Third, exposures to different types of obesogenic medications were examined separately for sulfonylureas, insulins, meglitinides, and antidepressants.

Outcome variables

We performed the analyses separately for weight- and fitness-change outcomes. We set the cutoff for a successful outcome based on the previous Look AHEAD study (12). For weight change, we used the following two cutoff points: medium to large weight loss (≥5% total weight loss) and large weight loss (≥10% total weight loss) from baseline to year 1. For fitness change, we used the following two cutoff points: medium to large fitness gain (≥1.0 Mets gain) and large fitness gain (≥2.0 Mets gain) from baseline to year 1.

Data analyses

Descriptive statistics were used to compare baseline characteristics of the participants according to exposures to obesogenic medications during the first year. *P* values were obtained using the pooled *t* test or Mann-Whitney test for continuous variables and χ^2 test for categorical variables.

For all analyses, we first calculated the crude odds ratio (OR), examining the association between exposures to obesogenic medications and weight or fitness changes in the overall population without the effect of the intervention. We then fitted multivariable logistic regression models, adjusting for race/ethnicity, baseline weight, baseline fitness, Beck Depression Inventory (BDI) score, and hypertension. Factors that varied across exposure groups at baseline but that did not show significance were eliminated from models using the backward elimination method (age, sex, education level, dyslipidemia, duration of diabetes, and use of leptogenic medication [alpha-glucosidase inhibitor, biguanide, orlistat, and sibutramine]). We tested interactions of randomization group by obesogenic medication exposures on each outcome.

All tests of hypotheses were two-sided and conducted at a 0.05 level of significance. All statistical analyses were performed using SAS University Edition (SAS Institute Inc., Cary, North Carolina), and the figures were generated by R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 5,145 randomly assigned participants in the Look AHEAD study, data from 4,906 participants were available in the NIDDK repository. We excluded 42 participants without medication information. For the

TABLE 1 Baseline characteristics in Look AHEAD study participants

	Weight-change outcome ($n = 4,496$)			Fitness-change outcome ($n = 4,051$)		
	Obesogenic med ($n = 3,199$)	No obesogenic med ($n = 1,297$)	*P* value[b]	Obesogenic med ($n = 2,852$)	No obesogenic med ($n = 1,199$)	*P* value[b]
Intensive lifestyle intervention study group, *n* (%)	1,603 (50.1)	683 (52.7)	0.12	1,452 (50.9)	636 (53.0)	0.22
Female, *n* (%)	1,837 (57.4)	776 (59.8)	0.14	1,627 (57.1)	711 (59.3)	0.19
Race/ethnicity, *n* (%)			0.14			0.19
Non-Hispanic white	2,108 (65.9)	880 (67.9)		1,900 (66.6)	829 (69.1)	
Non-Hispanic black	516 (16.1)	221 (17.0)		462 (16.2)	197 (16.4)	
Hispanic	459 (14.4)	156 (12.0)		387 (13.6)	136 (11.3)	
Other	116 (3.6)	40 (3.1)		103 (3.6)	37 (3.1)	
Age (y), mean (SD)	58.9 (6.7)	59.0 (6.8)	0.44	58.9 (6.7)	59.0 (6.8)	0.48
Baseline BMI (kg/m^2), mean (SD)	36.4 (5.9)	35.0 (5.8)	<0.0001	36.2 (5.8)	35.0 (5.8)	<0.0001
Baseline fitness (metabolic equivalents), mean (SD)	7.0 (1.9)	7.6 (2.0)	<0.0001	7.1 (1.9)	7.7 (2.0)	<0.0001
Duration of diabetes (y), median (q1, q3)	6 (3, 11)	3 (1, 5)	<0.0001	6 (3, 11)	3 (1, 5)	<0.0001
Hypertension, *n* (%)	2,769 (86.6)	1,001 (77.2)	<0.0001	2,442 (85.6)	917 (76.5)	<0.0001
Dyslipidemia, *n* (%)	2,293 (71.7)	871 (67.2)	<0.01	2,030 (71.2)	802 (66.9)	<0.01
Education level, *n* (%)			0.02			0.03
<13 years	639 (20.0)	220 (17.0)		553 (19.4)	201 (16.7)	
13-16 years	1,208 (37.8)	476 (36.7)		1,070 (37.5)	432 (36.0)	
>16 years	1,352 (42.3)	601 (46.3)		1,229 (43.1)	566 (47.2)	
BDI score ≥10, *n* (%)	583 (18.2)	148 (11.4)	<0.0001	510 (17.9)	133 (11.1)	<0.0001
Exposure to leptogenic medication[a], *n* (%)	2,273 (71.1)	788 (60.8)	<0.0001	2035 (71.4)	726 (60.6)	<0.0001

Data shown according to exposure to any obesogenic medication in first year.
Bold values denote *P*-value < 0.05.
[a]Alpha glucosidase inhibitor, biguanide, orlistat, and/or sibutramine.
[b]*P* values obtained with pooled *t* test or Mann-Whitney test for continuous variables and χ^2 test for categorical variables.
BDI, Beck Depression Inventory; med, medication.

weight-change outcome, 230 and 138 additional participants were excluded because of missing BMI and other covariates (duration of diabetes, education level, and BDI score), respectively, leaving an analytic sample size of 4,496. For the fitness-change outcome, 690 and 123 additional participants were excluded because of missing Mets information and other covariates, respectively, leaving an analytic sample size of 4,051.

For both weight-change and fitness-change outcomes, participants exposed to one or more obesogenic medications were more likely to have a higher mean BMI at baseline (36.4 vs. 35.0 for weight change and 36.2 vs. 35.0 for fitness change), have a longer median duration of diabetes (6 vs. 3 years for both outcomes), have BDI scores ≥ 10 (18.2% vs. 11.4% for weight change and 17.9% vs. 11.1% for fitness change), have hypertension and dyslipidemia, and take leptogenic medication (Table 1). The number of participants exposed to each obesogenic medication is reported in Supporting Information Table S1.

Weight-change outcome

Exposure to one or more obesogenic medications significantly decreased the odds of achieving medium and large weight loss by 32% (OR 0.68, 95% confidence interval [CI]: 0.58-0.80), adjusting for intervention, race/ethnicity, baseline BMI, hypertension, and BDI score (Figure 1 and Supporting Information Table S2). Similarly, exposure to obesogenic medications was associated with decreased odds of achieving large weight loss by 19%, regardless of the intervention (OR 0.81, 95% CI: 0.68-0.97) (Supporting Information Table S2). ILI intervention was positively associated with 5% or greater weight loss (OR 14.92). Other covariates negatively associated with 5% or greater weight loss were non-Hispanic black and other race/ethnicity (vs. non-Hispanic white, OR 0.59 and 0.49, respectively) and baseline BMI of 25 to 30 (vs. baseline BMI ≥ 4 , OR 0.74).

The association between obesogenic medications and weight loss was dose-dependent. The use of both one and two or more obesogenic medications was significantly associated with decreased odds of achieving medium/large and large weight loss (OR 0.73 and 0.58, 95% CI: 0.62-0.87 and 0.47-0.71, respectively) (Table 2). Using two or more medications further decreased the likelihood of achieving medium and large weight loss compared with using just one medication (data not shown, available upon request). Although using one medication was associated with a nonsignificant trend toward achieving large weight loss (OR 0.90, 95% CI: 0.75-1.09), using two or more medications was also significantly associated with decreased odds of achieving large weight loss (OR 0.63, 95% CI: 0.50-0.80).

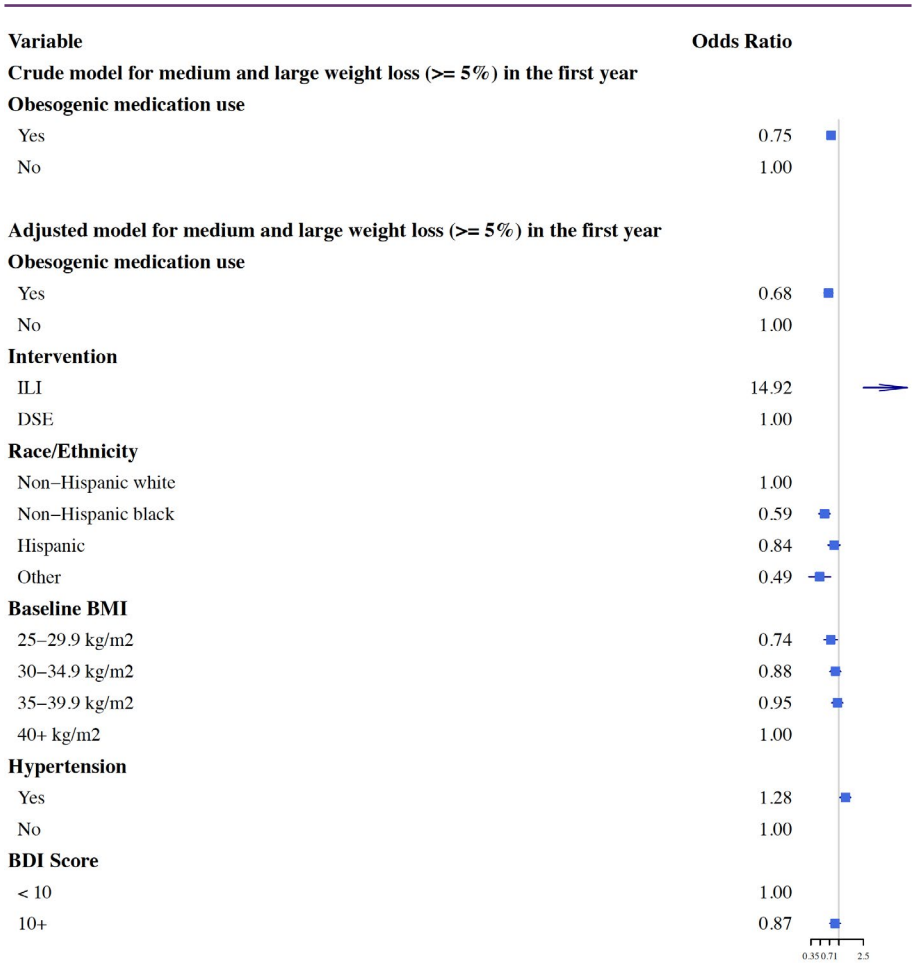

Figure 1 Weight outcome associated with exposures to obesogenic medications. BDI, Beck Depression Inventory; DSE, diabetes support and education; ILI, intensive lifestyle intervention. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Weight and fitness outcomes associated with different levels of exposure to obesogenic medications

	Weight-change outcome (percentage weight loss in first year; $n = 4{,}496$)			Fitness-change outcome (change in metabolic equivalents in first year; $n = 4{,}051$)		
Exposure	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	AUC[b]	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	AUC[b]
	Medium and large loss (≥5%)			*Medium and large gain (≥1 metabolic equivalents)*		
One medication use	**0.79 (0.69, 0.91)**	**0.73 (0.62, 0.87)**	0.82	**0.86 (0.75, 0.99)**	0.93 (0.79, 1.08)	0.67
Two+ medication use	**0.66 (0.56, 0.78)**	**0.58 (0.47, 0.71)**		**0.80 (0.67, 0.95)**	0.92 (0.76, 1.11)	
	Large loss (≥10%)			*Large gain (≥2 metabolic equivalents)*		
One medication use	0.91 (0.78,1.08)	0.90 (0.75, 1.09)	0.81	**0.82 (0.69, 0.97)**	0.90 (0.75, 1.07)	0.69
Two+ medication use	**0.80 (0.71, 0.90)**	**0.63 (0.50, 0.80)**		**0.69 (0.56, 0.85)**	0.83 (0.67, 1.04)	

Bold values denote $P < 0.05$.
[a]Adjusted for intervention status, race/ethnicity, hypertension, Beck Depression Inventory score, baseline weight (for weight-change models), and baseline fitness (for fitness-change models).
[b]AUC for adjusted OR.
AUC, area under the curve; CI, confidence interval; OR, odds ratio.

TABLE 3 Weight and fitness outcomes associated with exposure to different types of obesogenic medications

	Weight-change outcome (percentage weight loss in first year; $n = 4{,}496$)			Fitness-change outcome (change in metabolic equivalents in first year; $n = 4{,}051$)		
Exposure	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	AUC[b]	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	AUC[b]
	Medium and large loss (≥5%)			*Medium and large gain (≥1 metabolic equivalents)*		
Sulfonylureas	**0.79 (0.70, 0.89)**	**0.77 (0.66, 0.89)**	0.82	0.89 (0.79, 1.01)	0.95 (0.83, 1.08)	0.67
Insulins	**0.69 (0.59, 0.81)**	**0.69 (0.57, 0.85)**		0.92 (0.77, 1.09)	1.07 (0.89, 1.28)	
Meglitinides	0.74 (0.54, 1.01)	0.77 (0.52, 1.13)		0.98 (0.70, 1.35)	1.04 (0.74, 1.46)	
Antidepressants	0.96 (0.83, 1.12)	**0.82 (0.68, 0.98)**		0.86 (0.74, 1.01)	0.88 (0.74, 1.04)	
	Large loss (≥10%)			*Large gain (≥ 2 metabolic equivalents)*		
Sulfonylureas	0.92 (0.80, 1.06)	0.96 (0.81, 1.13)	0.82	0.88 (0.76, 1.03)	0.95 (0.81, 1.11)	0.69
Insulins	**0.80 (0.66, 0.98)**	0.88 (0.70, 1.10)		**0.74 (0.60, 0.91)**	0.87 (0.70, 1.08)	
Meglitinides	0.74 (0.50, 1.11)	0.78 (0.49, 1.23)		1.07 (0.74, 1.56)	1.17 (0.79, 1.72)	
Antidepressants	**0.75 (0.62, 0.90)**	**0.59 (0.48, 0.74)**		0.86 (0.71, 1.03)	0.91 (0.75, 1.11)	

Bold values denote $P < 0.05$.
[a]Adjusted for intervention status, race/ethnicity, hypertension, Beck Depression Inventory score, baseline weight (for weight-change models), and baseline fitness (for fitness-change models).
[b]AUC for adjusted OR.
AUC, area under the curve; CI, confidence interval; OR, odds ratio.

Sulfonylureas, insulins, and antidepressants were significantly associated with decreased odds of achieving 5% or greater weight loss in the adjusted model (Table 3) (OR 0.77, 0.69, and 0.82, respectively). However, only exposures to antidepressants were significantly associated with decreased odds of achieving 10% or greater weight loss (OR 0.59, 95% CI: 0.48-0.74), after adjusting for BDI scores and other covariates.

Fitness-change outcome

Exposure to one or more obesogenic medications was not significantly associated with the odds of achieving medium/large or large fitness gains (OR 0.93 and 0.88, 95% CI: 0.80-1.07 and 0.74-1.04, respectively), adjusting for intervention, race/ethnicity, baseline fitness level, hypertension, and BDI score (Figure 2 and Supporting Information Table S3). ILI intervention (OR 2.99) and greater baseline fitness level (by one Met, OR 1.13) were positively associated with fitness gain of one Met or greater. Other covariates negatively associated with fitness gain of two Mets or greater were non-Hispanic black race/ethnicity (vs. non-Hispanic white, OR 0.79) and BDI score ≥ 10 (OR 0.75).

The relationship between obesogenic medication exposure and fitness gain did not change when the outcome was stratified by dosage (Table 2) or the type of medication (Table 3).

Figure 2 Fitness outcome associated with exposures to obesogenic medications. BDI, Beck Depression Inventory; DSE, diabetes support and education; ILI, intensive lifestyle intervention; Mets: metabolic equivalents. [Color figure can be viewed at wileyonlinelibrary.com]

Sensitivity analyses

For sensitivity analyses, weight-change outcome analyses were stratified by each comorbidity associated with obesogenic medications in order to address the possible effect of comorbidity (depression and type 2 diabetes) influencing the outcome rather than the medication itself. Among participants with high BDI scores (≥10, $n=731$), exposure to obesogenic medications was associated with decreased odds of achieving 5% or greater weight loss by 39%, regardless of the intervention, race/ethnicity, baseline BMI, and hypertension (OR 0.61, 95% CI: 0.39-0.96). Among participants with a long duration of type 2 diabetes (≥5 years, $n=2,436$), exposure to obesogenic medications was associated with a smaller likelihood of achieving 5% or greater weight loss by 41%, regardless of the intervention, race/ethnicity, baseline BMI, and hypertension (OR 0.59, 95% CI: 0.44-0.77).

Discussion

In this post hoc analysis for the Look AHEAD trial, we demonstrated that exposures to obesogenic medications can drive the lack of trial effectiveness and thus interfere with both weight and fitness outcomes. These results were independent of other risk factors and they presented after adjustment for comorbidities and BDI scores. Additionally, we showed that the association between trial effectiveness on weight and exposures to obesogenic medications displayed a dose-dependent relationship. The association seemed to stem from exposures to medications rather than comorbidities that required the use of these medications (sensitivity analyses). These results highlight the importance of controlling for exposures to obesogenic medications when designing weight loss clinical trials.

The effect of obesogenic medications that we observed in this study is consistent with the current literature. In a systemic review, Domecq et al. (14) showed that atypical antipsychotics (e.g., olanzapine, quetiapine, risperidone), anticonvulsants and mood stabilizers (e.g., gabapentin, divalproex, carbamazepine), hypoglycemic agents (e.g., tolbutamide, glimepiride, gliclazide), and antidepressants (e.g., amitriptyline, mirtazapine) were associated with weight gain. Our results are supported by prior analyses from a recent retrospective case-control study, which found that the use of obesogenic medications was associated with a reduced likelihood (by 37%) of achieving 5% or greater weight loss after an 8-week behavioral weight management program (15). This

study also found that the response was dose-dependent, in which the likelihood of achieving weight loss was lesser among those who took more than one obesogenic medication.

A similar effect of obesogenic medications was observed among patients undergoing a bariatric procedure (sleeve gastrectomy). Leggett et al. (16) found that patients who were exposed to obesogenic medications had an 11.2% smaller mean percentage of excess weight loss after sleeve gastrectomy than those who were not. Their results showed that obesogenic medications interfere with weight loss significantly enough to modify the results of a behavioral intervention program as well as a bariatric procedure. The current study adds to the literature by showing that exposures to obesogenic medications were associated with poorer weight loss results for a randomized clinical weight loss trial as well.

Despite growing evidence for medication-induced weight, controlling measures for exposures to obesogenic medications in clinical trials are often underused. The Look AHEAD trial was not effective in reducing adverse cardiovascular events overall, but further analyses have shown that patients who lost weight in the trial showed improvements in their CVD event risk (12). Thus, the use of obesogenic medications could have been one of the culprits for impaired trial efficacy. It is also possible that subjects failed to maintain weight loss because of the introduction of obesogenic medications after enrollment. This study presents significant results supporting that controlling and accounting for obesogenic medications are important in weight loss trials. Furthermore, we showed that despite adjustment for depressive symptoms (using BDI scores), a potential confounding element for weight gain (25-28), antidepressant use was independently associated with a lower likelihood of achieving weight loss. We also showed that the use of leptogenic medications did not alter the association between the trial outcome and obesogenic medications, which suggests that obesogenic medications have a stronger effect than leptogenic medications.

Some limitations are worth mentioning. First, our study was a secondary data analysis—although the study was designed as a clinical trial, the trial was not focused on capturing obesogenic medication usage. This could have resulted in underreporting of the obesogenic medication use and possible misclassification bias. Also, the list of obesogenic medications was not as comprehensive as other studies that focused on obesogenic medications (15,16). Second, the exact duration and dosage of medication use were not available. Nevertheless, we used the number of obesogenic medications as a proxy for dosage; our results showed that the relationship between obesogenic medication use and weight loss outcome depended on the number of obesogenic medications. Third, the participants had diabetes and were 45 years old or older at enrollment. Although the duration of diabetes and age did not affect the association between obesogenic medication use and weight loss, the results from this study may not be generalized to a younger population without diabetes.

The outlook on obesity prevalence is grim (1). To stagnate and hopefully reverse the trend toward a population with greater obesity, we are in dire need of effective obesity intervention. For obesity interventions to be more successful, selecting optimal candidates for interventions would be necessary. This study suggests that obesogenic medication usage should be taken into account when selecting obesity intervention participants as well as interpreting the outcomes of an intervention.O

Disclosure: The authors declared no conflict of interest.

Supporting information: Additional Supporting Information may be found in the online version of this article.

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