Medical Management of Obesity in the Psychiatric Practice

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Excessive weight gain is a concern for most people, particularly patients who have psychiatric disorders. Many factors acting together contribute to obesity—including behavioral, environmental, psychological, genetic, and physiologic influences. Certain medications, such as antipsychotics and some antidepressants, can cause weight gain. Many clinicians consider excess body fat to be a cosmetic issue. However, obesity itself is a medical disease, comprising physical, biochemical, and psychological problems, and it must be managed along with one's other diseases, including psychiatric disorders.[1]

Obesity Overview

For diagnosis, obesity is traditionally classified by body mass index (BMI) (Table 1). BMI is a simple tool that is useful for tracking a patient's progress. However, a full assessment includes not only the extent of obesity but also the condition of the patient overall.[2]

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal Weight	18.5–24.9
Overweight	25.0–29.9
Obesity (Class 1)	30.0–34.9
Obesity (Class 2)	35.0–39.9
Extreme Obesity (Class 3)	≥40

Table 1: Obesity Classifications[2]

Obesity can have many medical comorbidities. These include biomechanical complications such as stress on weight-bearing joints, as well as tissue compression (eg, sleep apnea and gastrointestinal reflux) and rashes. Additionally, excess adipose tissue can become dysfunctional and result in deranged endocrine and immune responses. This can lead to dyslipidemia, hypertension, diabetes, and other metabolic diseases.[3]

Across the US, the incidence of obesity among adults in the last 20 years has increased from about 22% to 35%.[4] Among psychiatric patients in particular (eg, schizophrenia and depression), there is an even higher rate of obesity. One study found that 50% of female and 41% of male patients with severe mental illness were obese, compared to 27% of women and 20% of men in the matched comparison groups with no mental illness.[5]

Obesity in the Psychiatric Practice

There have been many connections observed between psychiatric disorders and obesity (Figure 1), and although causality is difficult to determine, the associations are striking. For example, epidemiologic studies have consistently found an association of binge eating disorder (BED) with obesity.[6] In clinical samples, up to 74% of patients with recent BED are overweight or obese,[7] and conversely, 30% of people seeking treatment for obesity have binge eating behavior.[8] Simon et al demonstrated significant positive associations between obesity and a range of mood and anxiety disorders.[9] One meta-analysis conducted by Luppino et al found bidirectional correlations between obesity and depression, such that obese persons have a 55% increased risk for onset of depression over time, and depressed adults have a 58% increased risk of becoming obese.[10] Pagoto et al found a significant link between obesity and post-traumatic stress disorder (PTSD). Among patients with PTSD within one year prior to analysis, 32.6% were obese, compared to 24.1% of those with no

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history of PTSD. Interestingly, this correlation was not mediated by BED, despite the known association of both PTSD and obesity with BED.[11] Finally, there is a very high rate of obesity among patients with bipolar disorder, and Fagiolini et al found that obesity is correlated with several indicators of a worsening prognosis and outcome in bipolar I disorder.[12]

Abdominal obesity, along with high fasting glucose and triglycerides, low high-density lipoprotein (HDL) cholesterol, and hypertension, characterizes metabolic syndrome. Development of the syndrome increases the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality. Puustinen et al examined the chance of developing metabolic syndrome over 5–7 years of follow-up based on baseline level of psychological distress, assessed by the General Health Questionnaire (GHQ-12). They found that patients with high psychological distress at baseline were more than twice as likely to develop metabolic syndrome as those with low psychological distress. Subanalyses suggested that differences in health behaviors and demographic characteristics do not alone explain this connection, and the researchers hypothesize that inflammation caused by psychological distress could be mediating the development of metabolic syndrome.[13]

Not only are psychiatric disorders associated with obesity, but psychiatric medications may also cause weight gain. Many tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are associated with weight gain as a side effect. Some selective serotonin reuptake inhibitors (SSRIs) are associated with early minimal weight loss only to be followed by long-term weight gain; bupropion may be one of the only antidepressants routinely associated with modest weight loss.[14] Furthermore, second-generation (atypical) antipsychotics may not only cause weight gain, but also appear in some cases to have an independent effect on glucose and lipid metabolism, putting patients who are using these medications at significant risk for developing obesity and metabolic syndrome.[15]

Figure 1: Associations Between Obesity and Psychiatric Disorders[6,9-13]

While many psychiatrists monitor patients for weight gain and its associated health concerns, given the demonstrated risk of patients with psychiatric disorders for obesity, diabetes, and dyslipidemia, *all* psychiatrists should carefully monitor their patients for these conditions. In 2004, the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity (now The Obesity Society) published a consensus statement on the connection between the use of antipsychotic drugs and obesity and diabetes. They advised close monitoring of weight and metabolic parameters, and stated that "patients' psychiatric illness should not discourage clinicians from addressing the metabolic complications for which these patients are at increased risk."[16] Despite these statements, however, adherence to their recommendations to screen patients remains low.[17]

Treatment Options for Obesity

For effective weight management, the treatment options should be tailored to each patient's individual needs. These approaches include lifestyle modifications, behavioral therapy, pharmacotherapy, and bariatric surgery. The initial consideration for each treatment should be made based on the patient's BMI (Table 2).[2]

The basis of any treatment for obesity includes improved nutrition and increased physical activity, along with behavioral therapy. Behavioral therapy should include frequent encounters with a medical professional.[3] Psychiatrists are uniquely positioned to provide behavioral therapy and ongoing support to their patients. Cognitive behavioral therapy can be effective to help patients lose weight initially; however, many physiological factors continue to challenge long-term weight maintenance.[18]

To overcome physiological factors, many guidelines recommend adding pharmacotherapy, such as lorcaserin, as an adjunct to lifestyle modification for chronic weight management.[3,19,20] Lorcaserin is a selective 5-HT_{2C} receptor agonist that is believed to promote satiety via the proopiomelanocortin neurons in the hypothalamus. The exact mechanism of action is not known.[21] Lorcaserin at the recommended daily dose selectively interacts with 5-HT_{2C} receptors as compared to 5-HT_{2A} and 5-HT_{2B} receptors, other 5-HT receptor subtypes, the 5-HT receptor transporter, and 5-HT reuptake sites. Thus, lorcaserin mimics the effect of serotonin in the hypothalamus, but does not increase serotonin levels.[21,22]

BMI Category (kg/m²)		Diet, Physical Activity, and Behavioral Therapy	Pharmacotherapy	Surgery
Overweight	**25.0–26.9**	Recommended with comorbidities		
	27.0–29.9		Recommended with comorbidities	
Obese	**30.0–34.9**	Recommended	Recommended	
	35.0–39.9			Recommended with comorbidities
	≥40			Recommended

Table 2: National Guidelines for Treating Obesity[2]

Lorcaserin is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m² or greater (obese), or 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, type 2 diabetes).[21]

The safety and efficacy of coadministration of lorcaserin with other products intended for weight loss, including prescription drugs (eg, phentermine), over-the-counter drugs, and herbal preparations, have not been established. The effect of lorcaserin on cardiovascular morbidity and mortality has not been established. Lorcaserin should not be taken during pregnancy or by women who are planning to become pregnant. Animal studies did not reveal evidence of teratogenicity with lorcaserin. A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese. See additional important safety information throughout.[21]

The concomitant use of lorcaserin with psychotropic agents, such as antidepressants and antipsychotics, has not been systematically evaluated and has not been established. Lorcaserin is not contraindicated in patients with psychiatric disorders or in concomitant use with antidepressants or antipsychotics. However, lorcaserin should be used with extreme caution when used with other serotonergic drugs due to the risk of serotonin syndrome.[21]

For more information on the use of lorcaserin in patients with psychiatric disorders, see page 7.

In clinical trials, patients with a recent history (within 1 or 2 years) of BED, major depression, anxiety, or other psychiatric disorder requiring prescription medication (eg, SSRIs, serotonin-norepinephrine reuptake inhibitors [SNRIs], bupropion, TCAs, antipsychotics, and lithium) were excluded. The use of SSRIs and SNRIs (including bupropion) for reasons other than active psychiatric indications (eg, migraine, weight loss, smoking cessation) required a 3-month washout.[23]

IMPORTANT SAFETY INFORMATION

Contraindication

- Lorcaserin should not be taken during pregnancy or by women who are planning to become pregnant.

Warnings and Precautions

- Lorcaserin is a serotonergic drug. The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported during use of serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors, tricyclic antidepressants, bupropion, triptans, dietary supplements such as St. John's Wort and tryptophan, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors), dextromethorphan, lithium, tramadol, antipsychotics or other dopamine antagonists, particularly when used in combination. Patients should be monitored for the emergence of serotonin syndrome symptoms or NMS-like reactions, including agitation, hallucinations, coma, tachycardia, labile blood pressure, hyperthermia, hyperreflexia, incoordination, nausea, vomiting, diarrhea, and muscle rigidity. Treatment with lorcaserin and any concomitant serotonergic or antidopaminergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.

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Clinical Trial Data With Lorcaserin

The safety and efficacy of lorcaserin for chronic weight management was studied in three long-term, Phase 3, randomized, double-blind, placebo-controlled trials. The primary efficacy parameter in all three trials was weight loss at one year, assessed by percent of patients achieving ≥5% and ≥10% weight loss and mean weight change. Secondary efficacy parameters included measurements of vital signs (blood pressure, heart rate), lipid parameters (HDL cholesterol, low-density lipoprotein [LDL] cholesterol, total cholesterol, triglycerides), and glycemic control (fasting glucose, fasting insulin, and, in patients with diabetes, hemoglobin A1c [HbA1c]).[21] Primary safety analysis included proportion of patients who developed new FDA-defined valvulopathy (mild or greater aortic valve regurgitation and/or moderate or greater mitral valve regurgitation) by Week 52.[24]

Patients received lorcaserin 10 mg BID or matching placebo BID. Additionally, all patients in the three trials received lifestyle modification counseling (the Healthy Lifestyle Program). Patients received one-on-one instruction with the first dose of study medication and then every four weeks throughout the trials.[21] Patients were advised to participate in moderate physical activity 30 minutes each day and to maintain a 600 kcal deficit based on individual estimates for daily energy requirements using World Health Organization criteria.[25]

BLOOM and BLOSSOM

The BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management)[25] and BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management)[26] trials included adults (age 18–65 years) with a BMI of 30–45 kg/m^2, or a BMI of 27–29.9 kg/m^2 with at least one weight-related comorbid condition (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea).[25,26] Because the two trials were similarly designed, the data are pooled.[21]

Among patients in the modified intent-to-treat population (mITT; all patients who received study medication and had a post-baseline measurement) using last-observation-carried-forward (LOCF) method, patients taking lorcaserin were more than twice as likely to lose ≥5% of their weight and more than 2.5 times more likely to lose ≥10% of their body weight than those taking placebo.[21] Results were also calculated for completer patients, all patients who completed a full year of study participation (Figure 2).[24] At Week 52, the mean weight loss was 5.8% with lorcaserin versus 2.5% with placebo in the mITT population (*P*<0.001); for completers, it was 8.0% with lorcaserin versus 3.7% with placebo.[21,24] Response to therapy should be evaluated by Week 12. If a patient has not lost at least 5% of body weight, discontinue BELVIQ, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.[21]

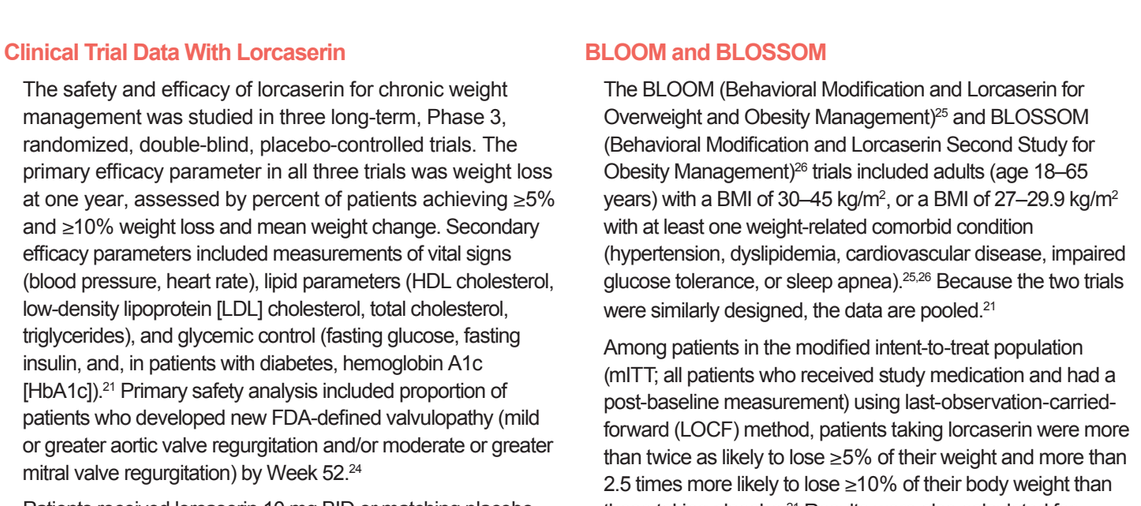

Figure 2: Patients Achieving Weight Loss at Week 52 in BLOOM/BLOSSOM[21,24]
* *P*<0.001.
† From the mITT population using LOCF method; all patients who received study medication and had a post-baseline measurement. 44% of patients taking lorcaserin and 51% of patients taking placebo withdrew prior to Week 52.
‡ From the completer population, all patients who completed a full year of study participation.

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Cardiometabolic parameters were also measured in the BLOOM and BLOSSOM trials (Table 3). Patients taking lorcaserin demonstrated greater improvement in systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, and fasting insulin compared to patients taking placebo. Other parameters, including blood pressure and heart rate, showed improvements consistent with what would be expected with weight loss in both groups.[21]

Parameter	Lorcaserin (N=3096)		Placebo (N=3039)		Lorcaserin Minus Placebo† (*P* Value)
	Baseline	Change From Baseline†	Baseline	Change From Baseline†	
Systolic Blood Pressure (mmHg)	121.4	-1.8	121.5	-1.0	-0.7 (*P*=0.007)
Diastolic Blood Pressure (mmHg)	77.4	-1.6	77.7	-1.0	-0.6 (*P*=0.003)
Heart Rate (bpm)	69.5	-1.2	69.5	-0.4	-0.8
Fasting Glucose (mg/dL)	92.1	-0.2	92.4	0.6	-0.8
Fasting Insulin‡ (µIU/mL)	15.9	-3.3	15.8	-1.3	-2.1 (*P*=0.0002)
Waist Circumference (cm)	109.3	-6.6	109.6	-4.0	-2.5
Parameter	**Baseline**	**% Change From Baseline†**	**Baseline**	**% Change From Baseline†**	**Lorcaserin Minus Placebo† (*P* Value)**
Total Cholesterol (mg/dL)	194.4	-0.9	194.8	0.4	-1.2 (*P*<0.001)
LDL Cholesterol (mg/dL)	114.3	1.6	114.1	2.9	-1.3 (*P*=0.015)
HDL Cholesterol (mg/dL)	53.2	1.8	53.5	0.6	1.2 (*P*=0.001)
Triglycerides (mg/dL)	135.4	-5.3	137.0	-0.5	-4.8 (*P*<0.001)

Table 3: Cardiometabolic Parameters at Week 52 in BLOOM/BLOSSOM*[21,24]
* mITT population using LOCF method; all patients who received study medication and had a post-baseline measurement. 44% of patients taking lorcaserin and 51% of patients taking placebo withdrew prior to Week 52.
† LSM adjusted for baseline value, treatment, study, and treatment by study interaction.
‡ Measured in BLOOM only (n=1538).

Limitation of Use

- The effect of lorcaserin on cardiovascular morbidity and mortality has not been established.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Patients should not take lorcaserin in combination with drugs that have been associated with valvular heart disease (eg, cabergoline). In clinical trials, 2.4% of patients taking lorcaserin and 2.0% of patients taking placebo developed valvular regurgitation: none of these patients were symptomatic. Lorcaserin should be used with caution in patients with congestive heart failure (CHF). Patients who develop signs and symptoms of valvular heart disease, including dyspnea, dependent edema, CHF, or a new cardiac murmur, should be evaluated and discontinuation of lorcaserin should be considered.
- Impairment in attention, memory, somnolence, confusion, and fatigue, have been reported in patients taking lorcaserin. Patients should not drive a car or operate heavy machinery until they know how lorcaserin affects them.
- The recommended dose of 10 mg twice daily should not be exceeded, as higher doses may cause euphoria, hallucination, and dissociation. Monitor patients for the development or worsening of depression, suicidal thoughts or behaviors, and/or any changes in mood. Discontinue lorcaserin in patients who develop suicidal thoughts or behaviors.

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BLOOM 2-Year Data

Modest weight loss can be beneficial for many patients, but only as long as it is maintained. Weight maintenance, however, is extremely difficult for many patients and lost weight is often regained over time. Relapse or success is often attributed to the patient's ability to adhere to the behavioral modifications he/she adopted to initially lose weight, but there are several potential mechanisms driving this behavior. Psychological factors believed to be associated with successful weight maintenance include[27]:

- Achieving a predetermined goal weight
- Successful coping strategies and problem-solving skills to deal with stressful situations
- Self-confidence in ability to control weight and food intake
- Vigilance in maintaining improved nutrition and physical activity
- Assessing efforts versus benefits of weight loss and maintenance

These attributes and techniques should be encouraged regularly when managing patients requiring chronic weight treatment.[27] Additionally, there are physiological factors to consider that complicate long-term weight maintenance. Biological changes that occur with weight loss and that can promote weight regain include changes in adipose cellularity, changes in energy metabolism, and altered neuroendocrine function. One potential result of these changes in endocrine function is decreased satiety and increased hunger.[28]

The BLOOM trial was designed as a 2-year study to examine the effect of lorcaserin on long-term weight maintenance.[21] Patients who completed the first year of the trial were eligible to continue on to Year 2.[25] At the start of the second year, patients taking lorcaserin were re-randomized to either continue lorcaserin or switch to placebo. Patients taking placebo continued on placebo.[21] The 2-year primary endpoint was the proportion of patients with ≥5% weight loss at the end of Year 1 who maintained ≥5% weight loss through Year 2.[25]

Of the 3182 patients who were randomized in Year 1, 1553 were randomized in Year 2; patients in all patient groups regained weight in Year 2 but remained below their Year 1 mean baseline weight. Among the completer population at the end of Year 2, patients taking lorcaserin for Year 1 and Year 2 lost 6.0 kg and patients who switched from lorcaserin in Year 1 to placebo in Year 2 lost 3.8 kg. Patients taking placebo for Year 1 and Year 2 lost 2.6 kg.[21] Analysis of the 2-year primary endpoint in the mITT population revealed that, among those taking lorcaserin who achieved ≥5% weight loss at the end of Year 1, 67.9% of patients who continued on lorcaserin maintained ≥5% weight loss over 2 years, versus 50.3% of those who switched to placebo (Figure 3).[25]

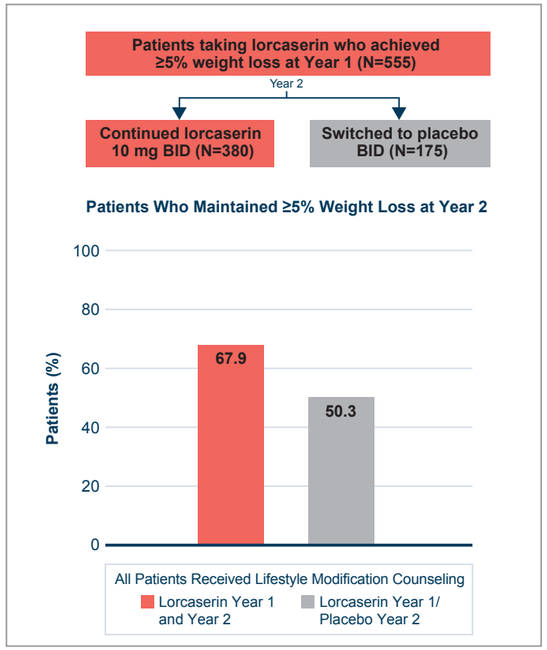

Figure 3: Patients Who Achieved and Maintained ≥5% Weight Loss at Year 2 in BLOOM*[23,24]

*Year 2 mITT population using LOCF method, all patients who received study medication and had a post-baseline measurement. 21.4% of patients taking lorcaserin and 29.7% of patients taking placebo withdrew prior to Week 104.

Using Lorcaserin in Patients With Psychiatric Disorders

Lorcaserin is not contraindicated in patients with psychiatric disorders or in concomitant use with antidepressants or antipsychotics.[21] However, there are some special considerations when using lorcaserin in this patient population.

In patients taking lorcaserin with other serotonergic agents (eg, SSRIs, SNRIs, TCAs, MAOIs, lithium, bupropion, triptans, dextromethorphan), extreme caution and careful observation is advised for the development of potentially life-threatening serotonin syndrome. Symptoms of serotonin syndrome may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia and incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuations in vital signs, and mental status changes.[21] The onset of serotonin syndrome is usually rapid and often accompanies the initial use, overdose, or dosing change of a medication that causes serotonin excess.[29] Treatment with lorcaserin and any concomitant serotonergic or antidopaminergic agents should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated.[21]

Patients using SSRIs, SNRIs, bupropion, TCAs, and MAOIs were excluded from the clinical trials with lorcaserin, but triptans and dextromethorphan were permitted. 2% and 1% of patients without diabetes and overweight patients with diabetes, respectively, used triptans concurrently; 15% and 12% of patients without diabetes and overweight patients with diabetes, respectively, used dextromethorphan concurrently at some point during clinical trials. Two patients treated with lorcaserin experienced a constellation of symptoms consistent with serotonin excess, including one patient on concomitant dextromethorphan who reported an adverse event of serotonin syndrome.[21]

Some drugs that target the central nervous system have been associated with depression or suicidal ideation.[21] Patients with a recent history of BED, major depression, anxiety, or other psychiatric disorders requiring prescription medication were excluded from clinical trials.[23] Patients were assessed using the Beck Depression Inventory-II at baseline and throughout the trials, and patients were monitored for new psychiatric events.[24] 2.6% of patients taking lorcaserin and 2.4% of patients taking placebo experienced depression or mood problems, and suicidal ideation occurred in 0.6% of patients taking lorcaserin and 0.4% of patients taking placebo. 1.3% and 0.6% of patients on lorcaserin and placebo, respectively, discontinued treatment due to depression-, mood-, or suicidal ideation-related events. All patients taking lorcaserin should be monitored for the emergence or worsening of depression, suicidal ideation, and/or any unusual changes in mood or behavior, and lorcaserin should be discontinued if they occur.[21]

BLOOM-DM

Over 85% of patients with type 2 diabetes are overweight or obese. However, it is even more difficult for patients with type 2 diabetes to lose weight than those without diabetes. The BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) trial was prospectively designed to study the safety and efficacy of lorcaserin for chronic weight management in patients with type 2 diabetes.[30]

Patients in BLOOM-DM were adults (age 18–65 years) with a BMI of 27–45 kg/m^2 and poorly controlled type 2 diabetes (HbA1c 7%–10%). All patients were being treated with metformin, a sulfonylurea, or both.[30]

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Among patients in the mITT population using LOCF method, patients taking lorcaserin were more than twice as likely to lose ≥5% of their weight and nearly four times more likely to lose ≥10% of their body weight than those taking placebo.[21] Results were also calculated for completer patients (Figure 4).[30]

At Week 52, the mean weight loss was 4.5% with lorcaserin versus 1.5% with placebo in the mITT population (P<0.001)[21]; for completers, the mean weight loss was 5.5% with lorcaserin versus 1.7% with placebo.[30]

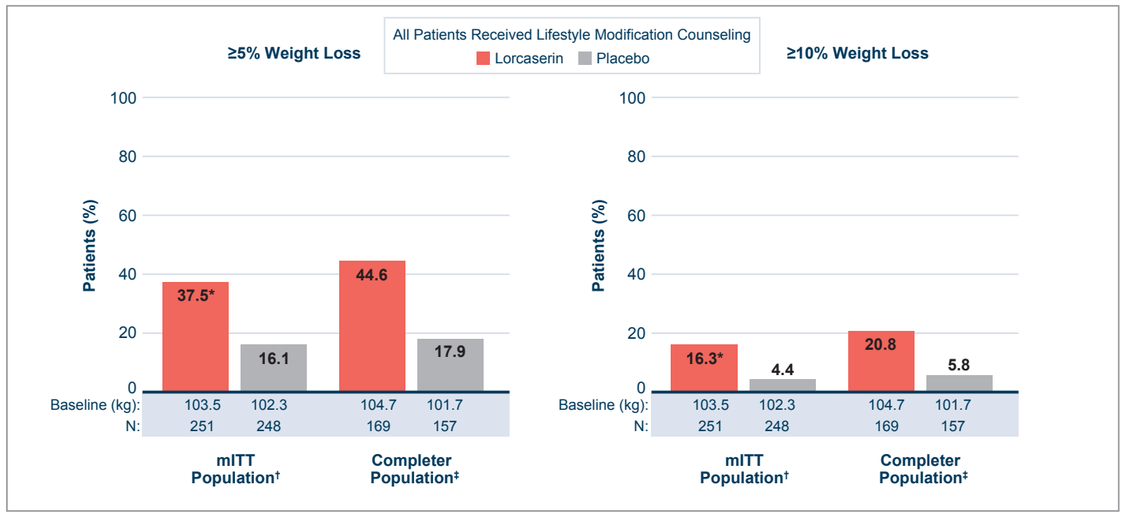

Figure 4: Patients Achieving Weight Loss at Week 52 in BLOOM-DM[21,30]
*P<0.001.
†From the mITT population using LOCF method; all patients who received study medication and had a post-baseline measurement. 34% of patients taking lorcaserin and 38% of patients taking placebo withdrew prior to Week 52.
‡From the completer population, all patients who completed a full year of study participation.

Limitation of Use

- The effect of lorcaserin on cardiovascular morbidity and mortality has not been established.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus who are being treated with antidiabetic medications, so measurement of blood sugar levels before and during treatment with lorcaserin is recommended. Decreases in doses of antidiabetic medications or changes in medication regimen should be considered.
- Men who experience priapism should immediately discontinue lorcaserin and seek emergency medical attention. Lorcaserin should be used with caution with erectile dysfunction medications. Lorcaserin should be used with caution in men who have conditions that might predispose them to priapism (eg, sickle cell anemia, multiple myeloma, or leukemia), or in men with anatomical deformation of the penis (eg, angulation, cavernosal fibrosis, or Peyronie's disease).
- Because lorcaserin may cause a slow heartbeat, it should be used with caution in patients with a history of bradycardia or heart block greater than first degree.
- Consider monitoring for CBC changes, prolactin excess, and pulmonary hypertension.

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An important consideration for patients with diabetes is improvement in glycemic control along with weight loss. In BLOOM-DM, patients in the mITT population taking lorcaserin demonstrated a 0.9% decrease in HbA1c levels and a 27.4 mg/dL decrease in fasting plasma glucose levels, compared to 0.4% and 11.9 mg/dL reductions, respectively, in patients taking placebo (Figure 5). Additionally, vital signs, lipid measurements, and waist circumference were assessed. Patients in both groups showed improvements in most of these parameters consistent with changes that typically accompany weight loss (Table 4).[21]

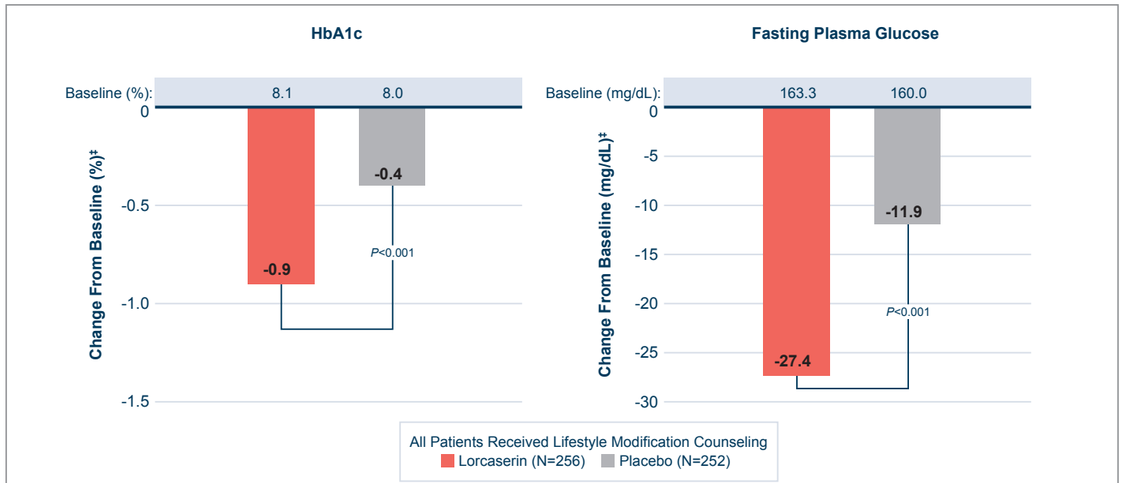

Figure 5: Changes in Parameters of Glycemic Control at Week 52 in BLOOM-DM*†[21,29]
*From the mITT population using LOCF method; all patients who received study medication and had a post-baseline measurement. 34% of patients taking lorcaserin and 38% of patients taking placebo withdrew prior to Week 52.
†Patients were already being treated with MET, SFU, or both.
‡Least squares means adjusted for baseline value, baseline HbA1c stratum, and prior antihyperglycemia medication stratum.

Parameter	Lorcaserin (N=256)		Placebo (N=252)		Lorcaserin Minus Placebo†
	Baseline	Change From Baseline†	Baseline	Change From Baseline†	
Systolic Blood Pressure (mmHg)	126.6	-0.8	126.5	-0.9	0.1
Diastolic Blood Pressure (mmHg)	77.9	-1.1	78.7	-0.7	-0.4
Heart Rate (bpm)	72.3	-2.0	72.7	-0.4	-1.6
Waist Circumference (cm)	115.8	-5.5	113.5	-3.3	-2.2
Parameter	**Baseline**	**% Change From Baseline†**	**Baseline**	**% Change From Baseline†**	**Lorcaserin Minus Placebo†**
Total Cholesterol (mg/dL)	173.5	-0.7	172.0	-0.1	-0.5
LDL Cholesterol (mg/dL)	95.0	4.2	94.6	5.0	-0.8
HDL Cholesterol (mg/dL)	45.3	5.2	45.7	1.6	3.6
Triglycerides (mg/dL)	172.1	-10.7	163.5	-4.8	-5.9

Table 4: Cardiometabolic Parameters at Week 52 in BLOOM-DM*[21]
*mITT population using LOCF method; all patients who received study medication and had a post-baseline measurement. 34% of patients taking lorcaserin and 38% of patients taking placebo withdrew prior to Week 52.
†LSM adjusted for baseline value, baseline HbA1c stratum, and prior antihyperglycemic medication stratum.

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Safety Assessment

Across all clinical trials of at least 1 year in duration, 6888 patients were evaluated, including 508 patients with type 2 diabetes. The overall discontinuation rate due to adverse reactions among patients taking lorcaserin (N=3451) was 8.6%, compared to 6.7% among those taking placebo (N=3437). The most common adverse reactions leading to discontinuation more often among patients treated with lorcaserin than placebo were headache (1.3% versus 0.8%), depression (0.9% versus 0.5%), and dizziness (0.7% versus 0.2%).[21] The overall most common adverse reactions among patients without diabetes and overweight patients with diabetes are shown in Tables 5 and 6. A key safety endpoint in all three trials was evaluation of valvular heart disease. Stimulation of the 5-HT_{2B} receptor has been associated with valvular heart disease. At therapeutic concentrations lorcaserin is selective for the 5-HT_{2C} receptor as compared to the 5-HT_{2B} receptor. The incidence of FDA-defined valvulopathy (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation) was assessed at Week 52; the incidence in patients taking lorcaserin was 2.4% and in patients taking placebo was 2.0%. None of these cases were symptomatic. The pooled relative risk of FDA-defined valvulopathy at Week 52 was 1.16 (95% Confidence Interval: 0.81–1.67) for lorcaserin versus placebo.[21]

Adverse Reaction	Lorcaserin (N=256)	Placebo (N=252)
Headache	16.8%	10.1%
Dizziness	8.5%	3.8%
Fatigue	7.2%	3.6%
Nausea	8.3%	5.3%
Dry Mouth	5.3%	2.3%
Constipation	5.8%	3.9%

Table 5: Most Common Adverse Reactions in Patients Without Diabetes[21]

Adverse Reaction	Lorcaserin (N=256)	Placebo (N=252)
Hypoglycemia	29.3%	21.0%
Symptomatic*	7.4%	6.3%
Headache	14.5%	7.1%
Back Pain	11.7%	7.9%
Cough	8.2%	4.4%
Fatigue	7.4%	4.0%

Table 6: Most Common Adverse Reactions in Overweight Patients With Diabetes[21]

*Any patient with blood sugar ≤65 mg/dL with symptoms. Not all patients required the assistance of another person.

Summary

Obesity is correlated with many psychiatric disorders, including but not limited to BED,[6] depression,[10] anxiety,[9] PTSD,[11] and bipolar disorder,[12] and should be managed along with these diseases. Initiation of a weight management treatment plan is essential for any overweight or obese patient, including those with psychiatric disorders.[1] Lifestyle modification and behavioral therapy are cornerstones of chronic weight management, but lorcaserin may be an appropriate adjunctive therapy for patients who are obese or overweight with weight-related comorbid conditions.[3,19,20] Lorcaserin has a novel mechanism of action that is believed to promote satiety, although the exact mechanism of action is not known. In clinical trials, all patients received lifestyle modification counseling, and compared to patients taking placebo, patients taking lorcaserin demonstrated greater weight loss at Year 1 and improved weight maintenance at Year 2.[21] Patients taking lorcaserin also showed significant improvements in glycemic control at Year 1, with HbA1c reduction of 0.9% versus 0.4% with placebo (P<0.001).[21,29] The most common adverse reactions of lorcaserin versus placebo in patients without diabetes were headache, dizziness, fatigue, nausea, dry mouth, and constipation; in patients with diabetes they were hypoglycemia, headache, back pain, cough, and fatigue.[21] As with many medications, special considerations should be taken when using lorcaserin in patients with psychiatric disorders.

IMPORTANT SAFETY INFORMATION

Warning and Precautions

- Patients should not take lorcaserin in combination with drugs that have been associated with valvular heart disease (eg, cabergoline). In clinical trials, 2.4% of patients taking lorcaserin and 2.0% of patients taking placebo developed valvular regurgitation: none of these patients were symptomatic. Lorcaserin should be used with caution in patients with congestive heart failure (CHF). Patients who develop signs and symptoms of valvular heart disease, including dyspnea, dependent edema, CHF, or a new cardiac murmur, should be evaluated and discontinuation of lorcaserin should be considered.

Nursing Mothers

- Lorcaserin should not be taken by women who are nursing.

Lorcaserin is a federally controlled substance (CIV) because it may be abused or lead to dependence.

Please see additional Important Safety Information presented throughout this paper.

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