Weight Loss Pharmacotherapy: Brief Summary of the Clinical Literature and Comments on Racial Differences

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The disparity in obesity rates between White, Black, and Hispanic individuals, especially women, is striking. Moreover, at any given body mass index or abdominal girth, incident diabetes is greater in Black, Hispanic and other racial-ethnic minorities than Whites. In addition to the growing health burden, the total costs of obesity in 2030 could exceed $500 billion (USD). Weight loss of 5%–15% from baseline can be attained with anti-obesity pharmacotherapy approved for long-term use in combination with lifestyle change. Weight loss of ≥5% is associated with medical benefits including reduction of incident diabetes and cardiovascular risk. While medical weight loss after one year or more in the US population is better than previously seen in many clinical trials, >60% of adults fail to sustain a 5% weight loss. Drug therapies approved for long-term weight loss may permit even more subjects to sustain healthful weight reduction. *Ethn Dis.* 2015;25(4):511-514; doi:10.18865/ed.25.4.511

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An estimated 154.7 million Americans aged > 20 years were overweight (76.3 million) or obese (89.4 million) based on data from the 2007–2010 National Health and Nutrition Examination Survey (NHANES).[1] While the prevalence of obesity was comparable among White, Black, and Hispanic men (33.8%, 37.9%, 36.0%, respectively), the disparity among White, Black, and Hispanic women was striking (32.5%, 53.9%, 44.8%). Given current trends, the total costs of obesity in 2030 could exceed $500 billion (USD).[2] The prevalence of cardiometabolic syndrome rises from roughly 5% to 25% then 50% as body mass index (BMI) increases from lean, to overweight, then obese range.[3] Incident diabetes is also strongly related to higher BMI and increased abdominal girth. Moreover, at any given body mass index or abdominal girth, incident diabetes is greater in Black, Hispanic and other racial-ethnic minorities than Whites.[4,5] Weight loss, especially combined with lifestyle modification including physical activity, is highly beneficial for reducing cardiometabolic risk and incident diabetes.[6,7]

While medical weight loss after one year or more in the US population is better than previously seen in many clinical trials, >60% of adults fail to sustain a 5% weight loss.[8] Since weight loss is very difficult to maintain, interest in pharmacotherapy as a long-term adjunct to lifestyle change has received strong interest. The 2013 Guideline for Management of Overweight and Obesity recommended consideration of pharmacological treatment options for obesity, ie, BMI ≥30 kg/m^2, and for overweight with BMI of 27.0–29.9 kg/m^2 when accompanied by comorbidities associated with excess body weight.[9] In general, pharmacotherapy as an adjunct to lifestyle change is associated with weight loss in the range of 5%–15%. Most of the weight loss is maintained as long as treatment is continued. This review summarizes the various classes of pharmacological agents approved for long-term weight loss in the United State, including effects on weight and associated cardiometabolic risk factors (Table 1).[10–14]

Given current trends, the total costs of obesity in 2030 could exceed $500 billion (USD).[2]

Previous studies on lifestyle interventions to promote weight loss also reported that White patients lost more weight than Black patients

Table 1. Descriptive characteristics of weight loss medications approved by the FDA for long-term use.[10–14,17,18]

Generic Name Year Approved	Mechanism	Wt Loss - Placebo	Δ SBP mm Hg	Lipids	Glucose	Adverse Effects	Cost / mo
Orlistat 1999 2007 OTC	Lipase inhibitor reduces fat absorption	2.5 – 3.4 kg	4 – 5 mm Hg decrease	TC, LDL-C, TG decline 10%	Fasting glucose, HbA1c and new onset DM decline	GI spotting, incontinence	$45 or more
Lorcaserin 2012	5-HT_{2C} receptor agonist decreases appetite	3.2 kg	1.5 mm Hg decrease	TG fall, HDL rises	Fasting glucose and HbA1c decline	Headache Dizzy/ Fatigue Constipation	$240
Phentermine – Topiramate 2012	Noradrenergic and GABA-receptor agonist decreases appetite	6.7 – 8.9 kg	2 – 3 mm Hg decline	TC and LDL-C fall 3%, TG decline 10%; HDL rises 6%	Small decline in fasting glucose, HbA1c	Paresthesia Dizzy, insomnia, Faster HR; changes in memory & cognition	$140 or more (generics off label)
Naltrexone / Bupropion 2014	Increase POMC which raises αMSH & beta endorphin; energy intake falls and output rises	5.5 – 10 kg	1 mm Hg increase	HDL rises 3 – 4%; LDL falls 4%	Fasting glucose declines 1 – 2 mg/dL	Paresthesia, Dry mouth, Constipation, dysgeusia, depression	$200
Liraglutide 2014	GLP-1 agonist increases satiety and reduces caloric intake	4 – 5 kg	2 – 3 mm Hg fall; HR rises 2–3 bpm	TC falls 10%, TG 10–20% and LDL 5 – 18%; HDL rises 5–18%	HbA1c declines 1 – 2% (absolute)	GI (N, V, D, C, pain, gas, hypoglycemia)	$250-$750

Wt, weight; SBP, systolic blood pressure; OTC, over the counter; HT, hydroxytryptamine; GABA, gamma aminobutyric acid; POMC, pre-opiomelanocortin; MSH, melanocyte-stimulating hormone; GLP, glucagon-like peptide; kg, kilogram; mm Hg, millimeter mercury; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; HgA1c, hemoglobin A1c; GI, gastrointestinal; HR, heart rate; bpm, beats per minute; N, nausea; V, vomiting; D, diarrhea; C, constipation.

in the control group.[15,16] Similar to findings in the studies with lorcaserin,[10–12] lifestyle interventions appeared to produce greater weight loss in White than Black subjects. When adjusted for difference in race-comparable control patients, the lifestyle interventions for weight loss were equally effective in Black and White volunteers.[15] Racial differences in the effectiveness of anti-obesity pharmacotherapy for primary and secondary outcomes are not as fully understood and serve as the focus of this review.

Limited data are available comparing Black and White participants in pharmacologic weight loss studies. Sibutramine, withdrawn from the market for safety concerns,[17] produced 1.7 kg greater weight loss in White than Black patients (-4.4 vs. -2.7 kg).[13] Orlistat was associated with .5 kg greater weight loss in White than Black volunteers (-2.8 vs. -2.3 kg), which was not statistically significant. The importance of reporting placebo-adjusted weight loss was noted in studies with lorcaserin, a 5-HT2C receptor agonist. White subjects lost 6.7 kg vs. 3.9 kg in Black and 3.4 kg in Hispanic subjects.[10,12] Placebo-adjusted weight loss was 3.2 kg in Whites, 2.7 kg in Blacks and 1.4 kg in Hispanics. The Black-White difference fell from 2.8 kg to .5 kg and the Hispanic-White difference from 3.4 kg to 1.8 kg with placebo-adjustment.[13] Although self-identified Blacks comprised ~15% of volunteers in recent trials with phentermine-topiramate and naltrexone-bupropion,[14,18,19] results were not reported by race.

While advances in knowledge are captured in obesity management guidelines,[9] translation of evidence to clinical practice is important for an increasing number of obese individuals. Among Blacks and Hispanics, prescription medication as a method for weight loss is least utilized.[20] In nearly 300 severely obese adults, defined by BMI ≥35 kg/m^2 and obesity-related risk factors or ≥40 kg/m^2 without

concomitant risk factors, 58% were trying to lose weight.[21] Approximately 10% were enrolled in a commercial weight loss program, while use of weight loss medications was virtually non-existent. Low income and non-White race adversely impacted use of commercial weight loss programs. Approximately half of study participants were interested in bariatric surgery and pharmacotherapy, yet only one in four recalled discussing surgery and one in three a conversation on pharmacotherapy for weight loss with their physician. The survey suggests that few severely obese adults are receiving medications or bariatric surgery to enhance their weight loss. Limited use of anti-obesity medications may reflect limited discussions between patients and their providers, which partially reflect other barriers, eg, the prior dearth of approved options for long-term use, high cost, and restricted insurance coverage.

When combined with a structured weight loss program, a 5%–15% reduction from baseline weight can be attained with anti-obesity drugs approved for long-term weight reduction.[25]

Although trials are increasingly including diverse population samples, these studies are likely underpowered to make meaningful comparisons by race-ethnicity, and this information is often not provided. Unanswered questions remain regarding differences by race-ethnicity in secondary outcomes, eg, metabolic and adverse effects.[22] The obese population is also heterogeneous with respect to duration of obesity, age, and comorbidities. [23] The distribution of metabolically active adipose tissue may influence the efficacy of weight loss pharmacotherapy by race/ethnicity.[22] The physical and social environment of the neighborhoods, eg, opportunities to exercise safely and access to healthy foods, may also contribute to differential outcomes by race-ethnicity. [24] Since obesity is often a chronic health condition, future clinical trials should assess longer-term maintenance of weight loss after the main study is completed. Prioritizing methodological issues related to greater inclusion, analysis and reporting of results by race/ethnicity and neighborhood may further our understanding of the effectiveness of anti-obesity pharmacotherapy that could translate into improved clinical care for high-risk groups.

In summary, there are currently five FDA-approved pharmacological therapies for long-term weight loss with four approved beginning in 2012. Additional novel drug therapies for weight loss are likely to be approved in the next five years.[25] When combined with a structured weight loss program, a 5%–15% reduction from baseline weight can be attained with anti-obesity drugs approved for long-term weight reduction.[25] Weight loss of ≥5% is associated with medical benefits including reduction of blood pressure, blood glucose level, risk of incident diabetes, and overall cardiovascular risk. While previous experience indicated that sustaining a ≥5% weight loss for five years was rare, a more recent analyses suggest a higher success rate. Yet, >60% of patients failed to achieve long-term weight loss of ≥5%.[8] Of note, >50% of subjects in the intensive lifestyle intervention arm of Look AHEAD achieved ≥5% weight loss at eight-years.[26] Drug therapies approved for long-term weight loss may permit even more individuals, including racial-ethnic minorities, to sustain healthful weight reduction.

Conflict of Interest

Author has received royalties from UpToDate, research support from Medtronic and Quintiles, and income as a consultant from AstraZeneca, Medtronic and Valencia. Second author has no disclosures.

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