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Pharmacologic Weight Loss: An Underutilized Practice in the Fight Against Obesity

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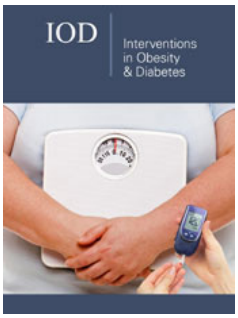

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Abstract

Obesity is considered one of the most contemporary threats to non-communicable disease such as cardiovascular disease, diabetes, musculoskeletal disorders and even some types of cancers. Its worldwide prevalence has nearly tripled between 1975 and 2016. In 2016, more than 1.9 billion adults aged 18 years and older were categorized as overweight, and of these over 650 million adults were obese. However, Weight management medications (WMM) are currently underutilized as an adjunct to behavioral and lifestyle interventions. By way of example, only 2% of eligible veterans received prescriptions for pharmacologic weight loss in the 2014-2015 fiscal years, and up to 1% of obese U.S. individuals filled a prescription for a WMM between 2009-2013. There are currently five FDA-approved medications for long-term weight loss medications. We analyzed 24 randomized clinical trials of the five drugs and interpreted findings. Of those 24, lorcaserin (Belviq®), naltrexone and bupropion (Contrave®), and phentermine and topiramate (Qsymia®) had four studies each, while liraglutide (Saxenda®), and orlistat (Xenical®) had six studies each. Underutilization of pharmacologic weight corrective therapies that have been statistically and clinically proven to be valuable tools in reducing obesity and its related risk factors. Studies of the five FDA-approved drugs have demonstrated clinically significant positive effects on weight loss with differing effects on both cardiovascular and glycemic markers/risk factors.

Keywords: Weight loss; Anti-obesity drugs; Obesity; Lorcaserin; Naltrexone and bupropion; Phentermine and topiramate;Liraglutide;Orlistat

Abbreviations: WHO: World Health Organization; MACE: Major Adverse Cardiovascular Events; BMI: Body Mass Index; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein

Introduction

Obesity epidemic

Obesity is considered one of the most serious contemporary threats to non-communicable diseases such as cardiovascular disease, diabetes, musculoskeletal disorders and even some types of cancers. Its worldwide prevalence has nearly tripled between 1975 and 2016. In 2016, more than 1.9 billion adults aged 18 years and older were categorized as overweight, and of these over 650 million adults were obese [1].

Current practice recommendations

The World Health Organization (WHO) has provided recommendations at both a societal and individual level: in order to reduce the obesity epidemic. At a societal level, WHO recommends supportive environments and communities that encourage healthy diet and exercise, whereas at the individual level, recommendations include limiting energy intake from total fats and sugars, increasing consumption of fruit and vegetables, as well as legumes, whole grains and nuts, and engaging in regular physical activity [1]. Thus, current first-line strategy for the treatment of obesity is through lifestyle interventions. Reducing in caloric intake to 500-1000 calories per day deficit, increasing physical activity to 150-200 minutes per week, and changes in health behaviors are core objectives. However, while lifestyle modification has long been considered a mainstay of therapy for obesity, it has only produced modest weight loss and no reduction in major adverse cardiovascular events (MACE) [2]. Many individuals are not able to achieve and maintain meaningful weight-loss though diet and exercise alone [3,4]. Possible explanations behind the insufficiency of diet and exercise alone are the human genetic component, compensatory behaviors, and poor perception of energy. To date, more than 400 different genes have been implicated in the causes of overweight or

obesity, although only a handful appear to be major players. Genes contribute to obesity in many ways, by affecting appetite, satiety, metabolism, food cravings, body-fat distribution, and the tendency to use eating as a way to cope with stress. Compensatory behaviors refer to adjustments people may unconsciously make after working out to offset the calories burned. One 2009 study demonstrated that people seem to increase their food intake post-physical activity either because they thought they burned off a lot of calories or because they were hungrier. Another review of studies from 2012 found that people generally overestimated how much energy exercise burned and ate more when they worked out. Energy balance is expressed by the equation: ES (Energy Store): the rate of changed body energy stores equals EI (Energy Intake): the rate of energy intake minus EE (Energy Expenditure). The rate of energy expenditures typically expressed in kcal per day [5].

Limitations to current practice quantitative measurements of overweight and obesity

Body mass index (BMI), is used by WHO to measure body size and as an indicator of high body fatness. BMI is calculated using a person's weight in kilograms divided by the square of their height in meters. According to the WHO definition, overweight is a BMI greater than or equal to 25; and obesity is a BMI greater than or equal to 30. It is a quick and convenient population-level measure of overweight and obesity due to its universality: the calculation does not change between males and females, nor does it discriminate on age. However, despite its usefulness: BMI should be considered a rough guide rather than a true body fatness measure, as it is not powered to account for human variation in anatomy.

The concept of clinically meaningful weight loss

The idea of quantitative measurement of obesity came in stages. Quetelet introduced BMI, which was applied nearly a century later to the evaluation of degree of fatness in studies of familial inheritance of obesity [6]. Publication of average weight tables in the 1850s was expanded to "ideal" weight tables by the life insurance industry in the mid-20th century. However, the relation of increasing weight to disease risk was extended by the Framingham Study from which Gordon and Kannel concluded that if everyone were at optimal weight, the incidence of coronary heart disease would be reduced by 25% and congestive failure and brain infarctions would be reduced by 35% [7]. By mid-1970's there had been many observations about the association of obesity and health issues. In 1973, the Fogarty Conference report suggested several criteria, including percent achieving 20- and 40-pound weight loss and a weight reduction index. Clearly the obvious question was, "What defines clinically significant weight loss?" Up to this point in time, few, if any, had suggested that modest weight losses might have important health benefits. In the 1980s, one approach to this question was based on defining clinically significant overweight as a body weight with a BMI>30. Thus, clinically significant weight loss would be reduction below a BMI of 30.

By the early 1990s, Rossner interpreted outcomes of treatment by percent weight loss. He concluded that <5% weight loss may reduce risk but was unsatisfactory, whereas a weight loss of 5-10% was considered a "fair" response [8]. In 1992, Goldstein recommended ≤10% weight loss to define clinically meaningful weight loss [9]. Blackburn in 1995 suggested that 5% might be a valid "single" criterion to assess significant weight loss [10]. Two landmark studies of diabetes prevention supported this recommendation. An average weight loss of 5.5% reduced the incidence of diabetes by 58% in the American Diabetes Prevention Program (ADPP) trial [11]. A systematic analysis of clinical trials with outcome data observed for at least 2 years by Douketis et al. [12] provided convincing evidence that 5% weight loss produced important improvements in risk factors or incidence of disease in populations "at risk" from their obesity [12]. A statistical model of the weight loss data from the ADPP trial by Hamman et al. [13] showed that for every kilogram of weight lost there was a 16% reduction in risk for progression to diabetes and that 5% weight loss would produce about 50% reduction in the incidence of type 2 diabetes [13]. Furthermore, a categorical analysis of weight loss from the Look AHEAD trial demonstrated a strong relationship between glycemic measures and weight loss, with improvement beginning at 2.5% to 5% weight loss. For systolic and diastolic blood pressure, high density lipoprotein (HDL) cholesterol, and triglycerides, improvement began at 5% weight loss. In 2013, an expert panel formed by the National Institutes of Health (NIH) conducted an evidence based review of the literature around five critical questions [14]. Critical question one addressed the health benefits of weight loss: "What amount weight loss is necessary to achieve benefit with respect to cardiovascular disease (CVD) risk factors, morbidity, and mortality?" The graded evidence statements that resulted from this effort provide the strongest support for weight loss beginning at 3% for glycemic measures and triglycerides, and 5% for blood pressure and HDL and low density lipoprotein (LDL) cholesterol, to be considered clinically meaningful. The committee went on to conclude that increased amounts of weight loss provided even greater benefits. To achieve improvement in systolic and diastolic blood pressure, HDL and LDL cholesterol, 5% or more weight loss from baseline is considered meaningful, while for glycemic measures and triglycerides, ≥3% weight loss is considered clinically significant [15].

Underutilization of pharmacologic corrective therapies

Weight management medications (WMM) are currently underutilized as an adjunct to behavioral and lifestyle interventions. By way of example, only 2% of eligible veterans received prescriptions for pharmacologic weight loss in the 2014-2015 fiscal years, and up to 1% of obese U.S. individuals filled a prescription for a WMM between 2009-2013. In addition, physician prescribing patterns have been declining, with the exception of phentermine, since 1991. Possible explanations for the WMM prescribing downtrend include absence of physician training

in pharmacotherapy for obesity and impediments by the U.S. healthcare system such as lack of insurance coverage or limited patient-provider time for discussing interventions [16,17].

Examine the five US FDA-approved medications for long-term weight loss

There are five FDA-approved weight loss medications for long-term use. See Table 1 for detail.

Methods

We analyzed 24 randomized clinical trials of the five weight loss drugs and interpreted findings. Of those 24, lorcaserin (Belviq®), naltrexone and bupropion (Contrave®), and phentermine and topiramate (Qsymia®) had four studies each, while liraglutide (Saxenda®), and orlistat (Xenical®) had six studies each [18-22]. There were 21 double-blind, 22 placebo-controlled, 3 open-label and 11 multiple-arm studies evaluated. In addition, 54% were post-market, while 38% and 8% were Phase III and Phase II trials, respectively. The published journals and numbers of trials are as follows: Obesity Journal: 5, International Journal of Obesity: 4, The Lancet: 3, JAMA: 3, Journal of Clinical Endocrinology and Metabolism: 2, and 1 trial evaluated each for the Current Therapeutic Research Journal, Sleep Journal, Diabetes Care, New England Journal of Medicine, Diabetes, Obesity and Metabolism, Archives of Medical Science and American Journal of Clinical Nutrition. The summary of each characteristics of weight loss drugs are shown in Table 1.

Table 1: Five US FDA approved drugs for long-term weight loss.

Adverse Effects	Oily Spotting Flatus with discharge Fecal urgency Increased defecation and fecal incontinence	Paraesthesia Dizziness Insomnia Constipation Dysgeusia Constipation	Headache Dizziness Nausea Dry Mouth Constipation Hypoglycemia	Headache Dizziness Nausea Dry Mouth Constipation Insomnia	Headache Dizziness Nausea Dry Mouth Constipation Hypoglycemia
Contraindications	Pregnancy Chronic Malabsorption Syndrome Cholestasis Known Hypersensitivity to Xenical®	Pregnancy Glaucoma Hyperthyroidism During or within 14 days of monoamine oxidase inhibitor Known Hypersensitivity or idiosyncrasy to sympathomimetic amines	Pregnancy	Pregnancy Uncontrolled HTN Seizure disorders Chronic Opioid use MAOI inhibitors	Pregnancy Hypersensitivity to liraglutide or any product components Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2
Indications	For obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet To reduce the risk for weight regain after prior weight loss	Adjunct to a reduced-caloric diet and increased physical activity for chronic weight management in adults with an initial BMI of ≥30kg/m^2 or ≥27kg/m^2 in the presence of at least one weight-related co-morbidity such as HTN, T2DM or DLD	Adjunct to a reduced-caloric diet and increased physical activity for chronic weight management in adults with an initial BMI of ≥30kg/m^2 or ≥27kg/m^2 in the presence of at least one weight-related co-morbidity such as HTN, T2DM or DLD	Adjunct to a reduced-caloric diet and increased physical activity for chronic weight management in adults with an initial BMI of ≥30kg/m^2 or ≥27kg/m^2 in the presence of at least one weight-related co-morbidity such as HTN, T2DM or DLD	Adjunct to a reduced-caloric diet and increased physical activity for chronic weight management in adults with an initial BMI of ≥30kg/m^2 or ≥27kg/m^2 in the presence of at least one weight-related co-morbidity such as HTN, T2DM or DLD

Dose	One 120-mg capsule three times a day with each fatty meal	Take once daily in morning. Avoid evening dose to avoid insomnia.	Take 10mg twice daily D/C if 5% WL not achieved by week 12	Week 1 1tab qam, week 2 1 tab BID, week 3 2 tab qam 1tab qpm, week 4 2 tabs BID	3mg SQ daily. Initiate at 0.6mg per day for one week. In weekly intervals increase the dose until a dose of 3mg is reached.
Drug Category	Reversible Inhibitor of Gastrointestinal Lipases	PHEN: Sympathomimetic amine anorectic TOP: Antiepileptic	Serotonin 2C receptor agonist	NAL: An opioid antagonist BUP: Aminoketone antidepressant	Glucagon-like peptide-1 (GLP-1) receptor agonist
Drug Approved Year	Xenical® (orlistat)18 1999	Qsymia® (phentermine and topiramate)19 2012	Belviq® (lorcaserin)20 2012	Contrave® (naltrexone and bupropion)21 2014	Saxenda® (liraglutide)22 2014

Results

Xenical® (orlistat)

We selected six Xenical® studies for review, conducted by Davidson et al. [23-28] respectively (Table 2). 23-28 Five out of 6 studies demonstrated statistically significant weight loss and four out of six Xenical studies demonstrated clinically significant weight loss. For waist circumference measurement, two out of three Xenical studies led to statistically significant values versus control. Two out of two studies demonstrated statistically significant reduction in blood pressure while one out of two studies demonstrated statistically significant differences in fasting blood sugar versus control. In regard to cholesterol, four out of four studies demonstrated statistically significant reductions in total and LDL cholesterol, however, non-statistically significant variation was noted with triglycerides. Unfavorable yet statistically significant increase in HDL cholesterol was seen in comparison of Xenical and control group (Table 3).

Table 2: Selected studies for Xenical®.

Primary Author	Year	Journal	Sample Size	Study Length
Davidson M.H.	1999	JAMA	892 Participants	24 Months
Finer N.	2000	International Journal of Obesity	218 Participants	12 Months
Muls E.	2001	International Journal of Obesity	290 Participants	6 Months
Ozcelik O.	2004	Current Therapeutic Research	24 Participants	3 Months
Torgerson J.S.	2004	Diabetes Care	3305 Participants	48 Months
Kuhawska-tuczak M.	2017	Archives of Medical Science	73 Participants	3 Months

Table 3: Results of studies for Xenical®.

Primary Author	D WT Difference	C WT Difference	WT B/W Group P-value
Kuhawska-tuczak [28]	-9.4kg	-4.9kg	≤0.05
Ozcelik [26]	-6.76kg	-9kg	NS
Torgerson [27]	-5.8kg	-3kg	≤0.001
Finer [24]	-3.29kg	-1.31kg	≤0.01
Muls [25]	-4.66kg	-1.88kg	≤0.001
Davidson [23]	-3.2kg	5.63kg	≤0.001
Primary Author	**D WC Difference**	**C WC Difference**	**WC B/W Group P value**
Kuhawska-tuczak [28]	-10.5cm	-5.8cm	≤0.05
Torgerson [27]	-6.4cm	-4.4cm	≤0.01
Finer [24]	-6.3cm	-5.1cm	NS

Primary Author	D SBP Difference	C SBP Difference	SBP B/W Group P value
Torgerson [27]	-4.9mmHg	-3.4mmHg	≤0.01
Davidson [23]	-0.8mmHg	1mmHg	≤0.01
Primary Author	**D DBP Difference**	**C DBP Difference**	**DBP B/W Group P value**
Torgerson [27]	-2.6mmHg	-1.9mmHg	≤0.01
Davidson [23]	-0.5mmHg	1.3mmHg	≤0.01
Primary Author	**D FBG Difference**	**C FBG Difference**	**FBG B/W Group P value**
Kuhawska-tuczak [28]	0.31mg/dL	0.09mg/dL	NS
Torgerson [27]	1.8mg/dL	3.6mg/dL	≤0.01
Primary Author	**D TC Difference**	**C TC Difference**	**TC B/W Group P value**
Torgerson [27]	-17.72mg/dL	-5.16mg/dL	≤0.01
Finer [24]	-1.93mg/dL	11.6mg/dL	≤0.001
Muls [25]	-16.24mg/dL	5.41mg/dL	≤0.001
Davidson [23]	-5.02mg/dL	3.09mg/dL	≤0.05
Primary Author	**D LDL Difference**	**C LDL Difference**	**LDL B/W Group P value**
Torgerson [27]	-18.31mg/dL	-7.49mg/dL	≤0.01
Finer [24]	-4.25mg/dL	8.12mg/dL	≤0.001
Muls [25]	-20.5mg/dL	-3.48mg/dL	≤0.001
Davidson [23]	-5.41mg/dL	8.9mg/dL	≤0.05
Primary Author	**D HDL Difference**	**C HDL Difference**	**HDL B/W Group P value**
Torgerson [27]	3mg/dL	4.2mg/dL	0.01
Finer [24]	1.11mg/dL	1.08mg/dL	NS
Muls [25]	2.7mg/dL	6.2mg/dL	0.001
Primary Author	**D TG Difference**	**C TG Difference**	**TG B/W Group P value**
Torgerson [27]	4.04mg/dL	4.89mg/dL	NS
Muls [25]	7.09mg/dL	12.4mg/dL	NS

Qsymia® (phentermine and topiramate)

For Qsymia®, we reviewed four studies conducted by Allison et al. [29-32] & (Table 4). Four out of four Qsymia studies demonstrated statistically and clinically significant weight loss and three out of three studies measuring waist circumference led to statistically significant values compared to control group. Three out of four studies demonstrated statistically significant reductions in systolic blood pressure, two out of four demonstrated statistically significant reductions in fasting blood sugar and one demonstrated significant reductions in C-reactive protein. For cholesterol reduction, two out of three studies demonstrated statistically significant differences in total cholesterol, one out of four studies demonstrated unfavorable statistically significant differences in LDL cholesterol. Two out of four demonstrated statistically significant differences in HDL cholesterol (one favorable and one unfavorable), and two out of four studies demonstrated statistically significant differences in triglycerides. All results are summarized in Table 5.

Table 4: Selected studies for Qsymia®.

Primary Author	Year	Journal	Sample Size	Study Length
Allison D.B.	2011	Obesity Journal	1269 Participants	14 Months
Gadde K.M.	2011	The Lancet	2487 Participants	14 Months
Garvey W.T.	2012	American Journal of Clinical Nutrition	676 Participants	14 Months
Winslow D.H.	2012	Sleep Journal	45 Participants	7 Months

Table 5: Results of studies for Qsymia®.

Primary Author	Drug WT Difference	Control WT Difference	WT B/W Group P-value
Garvey [31]	-9.495kg	-1.82kg	≤0.0001
Allison [29]	-6.04kg	-1.795kg	≤0.0001
Winslow [32]	-11kg	-4.5kg	≤0.001
Gadde [30]	-8.1kg	-1.4kg	≤0.0001
Primary Author	**Drug WC Difference**	**Control WC Difference**	**WC B/W Group P value**
Garvey [31]	-9.8cm	-3.6cm	≤0.0001
Allison [29]	-5.6cm	-3.1cm	≤0.001
Gadde [30]	-7.6cm	-2.4cm	≤0.0001
Primary Author	**Drug WC Difference**	**Control WC Difference**	**WC B/W Group P value**
Garvey [31]	-9.8cm	-3.6cm	≤0.0001
Allison [29]	-5.6cm	-3.1cm	≤0.001
Gadde [30]	-7.6cm	-2.4cm	≤0.0001
Primary Author	**Drug SBP Difference**	**Control SBP Difference**	**SBP B/W Group P value**
Garvey [31]	-4.7mmHg	-3.2mmHg	NS
Allison [29]	-1.8mmHg	-2.9mmHg	≤0.001
Winslow [32]	-15mmHg	-7.3mmHg	≤0.05
Gadde [30]	-4.7mmHg	-2.4mmHg	≤0.001
Primary Author	**Drug DBP Difference**	**Control DBP Difference**	**DBP B/W Group P value**
Garvey [31]	-3.7mmHg	-3.9mmHg	NS
Allison [29]	-0.1mmHg	0.4mmHg	NS
Winslow [32]	-6.3mmHg	-5.6mmHg	NS
Gadde [30]	-3.4mmHg	-2.7mmHg	NS
Primary Author	**Drug FBG Difference**	**Control FBG Difference**	**FBG B/W Group P value**
Garvey [31]	0.1mg/dL	3.7mg/dL	NS
Allison [29]	-1.6mg/dL	1.9mg/dL	≤0.0001
Winslow [32]	-8.9mg/dL	-5.6mg/dL	NS
Gadde [30]	-0.18mg/dL	2.34mg/dL	≤0.005
Primary Author	**Drug hs-CRP Difference**	**Control hs-CRP Difference**	**hs-CRP B/W Group P value**
Gadde [30]	-2.49mg/dL	-0.79mg/dL	≤0.0001
Primary Author	**Drug TC Difference**	**Control TC Difference**	**TC B/W Group P value**
Allison [29]	-10.589mg/dL	-6.79mg/dL	≤0.05
Winslow [32]	-13.9mg/dL	-6.2mg/dL	NS
Gadde [30]	-9.85mg/dL	-6.76mg/dL	≤0.05
Primary Author	**Drug LDL Difference**	**Control LDL Difference**	**LDL B/W Group P value**
Garvey [31]	-5.598mg/dL	-13.172mg/dL	≤0.05
Allison [29]	-9.43mg/dL	-6.67mg/dL	NS
Winslow [32]	-11mg/dL	-1.6mg/dL	NS
Gadde [30]	-4.44mg/dL	-5.07mg/dL	NS
Primary Author	**Drug HDL Difference**	**Control HDL Difference**	**HDL B/W Group P value**
Garvey [31]	3.55mg/dL	2.33mg/dL	NS
Allison [29]	0.251mg/dL	0mg/dL	NS
Winslow [32]	-1.1mg/dL	2.3mg/dL	≤0.05
Gadde [30]	2.61mg/dL	0.6mg/dL	≤0.0001

Primary Author	Drug TG Difference	Control TG Difference	TG B/W Group P value
Garvey [31]	-19.65mg/dL	0.6176mg/dL	≤0.001
Allison [29]	6.068mg/dL	10.81mg/dL	NS
Winslow [32]	-32.4mg/dL	-33mg/dL	NS
Gadde [30]	-13.71mg/dL	7.49mg/dL	≤0.0001

Belviq (lorcaserin)

We reviewed four Belviq® clinical studies conducted by Fidler et al. [33-36] & (Table 6). Three out of four studies demonstrated statistically and clinically significant weight loss, and two out of three studies measuring waist circumference led to statistically significant values versus control. One out of four studies demonstrated statistically significant reductions in blood pressure and significant fasting blood sugar. No difference has been seen on C-reactive protein value while one out of three studies demonstrated statistically significant differences in triglycerides. Results are shown in Table 7.

Table 6: Selected studies for Belviq®.

Primary Author	Year	Journal	Sample Size	Study Length
Fidler M.C.	2011	Journal of Clinical Endocrinology and Metabolism	4004 Participants	13 Months
O'Neil P.M.	2012	Obesity Journal	603 Participants	24 Months
Smith S.R.	2017	Obesity Journal	238 Participants	3 Months
Tronieri J.S.	2018	Obesity Journal	137 Participants	12 Months

Table 7: Results of studies for Belviq®.

Primary Author	Drug WT Difference	Control WT Difference	WT B/W Group P-value
Fidler [33]	-5.8kg	-2.9kg	≤0.001
Tronieri [36]	-8.4kg	-6.1kg	NS
Smith [35]	-3.5kg	-7kg	≤0.05
O'Neil [34]	-4.7kg	-1.6kg	≤0.001
Primary Author	**Drug WC Difference**	**Control WC Difference**	**WC B/W Group P value**
Fidler [33]	-6.3cm	-4.1cm	≤0.001
Smith [35]	-3.4cm	-4.7cm	NM
O'Neil [34]	-5.5cm	-3.3cm	≤0.001
Primary Author	**Drug SBP Difference**	**Control SBP Difference**	**SBP B/W Group P value**
Fidler [33]	-1.9mmHg	-1.2mmHg	NS
Tronieri [36]	-1.6mmHg	-7.6mmHg	NS
Smith [35]	-5.5mmHg	-3.3mmHg	≤0.05
O'Neil [34]	-0.8mmHg	-0.9mmHg	NS
Primary Author	**Drug DBP Difference**	**Control DBP Difference**	**DBP B/W Group P value**
Fidler [33]	-1.9mmHg	-1.4mmHg	NS
Tronieri [36]	-1.4mmHg	-2.6mmHg	NS
Smith [35]	-2.5mmHg	-1.4mmHg	≤0.05
O'Neil [34]	-1.1mmHg	-0.7mmHg	NS
Primary Author	**Drug FBG Difference**	**Control FBG Difference**	**FBG B/W Group P value**
Tronieri [36]	1.4mg/dL	4mg/dL	NS
O'Neil [34]	-27.4mg/dL	-11.9mg/dL	≤0.001
Primary Author	**Drug hs-CRP Difference**	**Control hs-CRP Difference**	**hs-CRP B/W Group P value**
Tronieri [36]	-2.6mg/dL	-1.7mg/dL	NS
O'Neil [34]	-1.3mg/dL	-0.6mg/dL	NS

Primary Author	Drug TC Difference	Control TC Difference	TC B/W Group P value
Fidler [33]	-0.7mg/dL	0mg/dL	NS
Tronieri [36]	-7.8mg/dL	-7.5mg/dL	NS
O'Neil [34]	-0.7mg/dL	-1.7mg/dL	NS
Primary Author	**Drug LDL Difference**	**Control LDL Difference**	**LDL B/W Group P value**
Fidler [33]	0.3mg/dL	1.7mg/dL	NS
Tronieri [36]	-8mg/dL	-6.1mg/dL	NS
O'Neil [34]	4.2mg/dL	5mg/dL	NS
Primary Author	**Drug TG Difference**	**Control TG Difference**	**TG B/W Group P value**
Fidler [33]	-4.3mg/dL	-0.9mg/dL	≤0.05
Tronieri [36]	-5.5mg/dL	-5.3mg/dL	NS
O'Neil [34]	-10.7mg/dL	-4.8mg/dL	NS

Contrave® (naltrexone and bupropion)

We selected four Contrave® studies for review conducted by Greenway et al. [37-40] & (Table 8). Four out of four studies demonstrated statistically and clinically significant weight loss, and four out of four studies measuring waist circumference led to statistically significant values versus control. Two out of three studies demonstrated statistically significant reductions in blood pressure, two out of three demonstrated statistically significant reductions in fasting blood sugar and two studies demonstrated significant reductions in C-reactive protein. One study demonstrated total cholesterol reduction and one out of three studies demonstrated statistically significant reduction in LDL cholesterol. Two out of three studies demonstrated statistically significant differences in HDL cholesterol while three out of three studies demonstrated statistically significant differences in triglycerides. Results are summarized in Table 9.

Table 8: Selected studies for Contrave®.

Primary Author	Year	Journal	Sample Size	Study Length
Greenway F.L.	2009	Journal of Clinical Endocrinology and Metabolism	203 Participants	12 Months
Greenway F.L.	2010	The Lancet	1742 Participants	14 Months
Apovian C.M.	2013	Obesity Journal	1496 Participants	14 Months
Nissen S.E.	2016	JAMA	8905 Participants	48 Months

Table 9: Results of studies for Contrave®.

Primary Author	Drug WT Difference	Control WT Difference	WT B/W Group P-value
Nissen [40]	-3.9kg	-1.2kg	≤0.001
Greenway [38]	-5.1kg	-0.9kg	≤0.05
Apovian [39]	-6.2kg	-1.3kg	≤0.001
Greenway [37]	-6.1kg	-1.3kg	≤0.0001
Primary Author	**Drug WC Difference**	**Control WC Difference**	**WC B/W Group P value**
Nissen [40]	-2.1cm	-0.8cm	≤0.001
Greenway [38]	-5.4cm	-1cm	≤0.05
Apovian [39]	-6.7cm	-2.1cm	≤0.001
Greenway [37]	-6.2cm	-2.5cm	≤0.0001
Primary Author	**Drug SBP Difference**	**Control SBP Difference**	**SBP B/W Group P value**
Greenway [38]	-1.6mmHg	-1mmHg	NS
Apovian [39]	0.6mmHg	-0.5mmHg	≤0.05
Greenway [37]	-0.1mmHg	-1.9mmHg	≤0.001
Primary Author	**Drug DBP Difference**	**Control DBP Difference**	**DBP B/W Group P value**
Greenway [38]	-1.2mmHg	-4.4mmHg	NS
Apovian [39]	0.4mmHg	0.3mmHg	NS

Greenway [37]	0mmHg	-0.9mmHg	≤0.01
Primary Author	**Drug FBG Difference**	**Control FBG Difference**	**FBG B/W Group P value**
Greenway [38]	-2mg/dL	1.9mg/dL	NS
Apovian [39]	-2.8mg/dL	-1.3mg/dL	≤0.05
Greenway [37]	-3.24mg/dL	-1.26mg/dL	≤0.0001
Primary Author	**Drug hs-CRP Difference**	**Control hs-CRP Difference**	**hs-CRP B/W Group P value**
Apovian [39]	-1.09mg/dL	-0.307mg/dL	≤0.001
Greenway [37]	-1.11mg/dL	-0.596mg/dL	≤0.01
Primary Author	**Drug TC Difference**	**Control TC Difference**	**TC B/W Group P value**
Greenway [38]	-9.5mg/dL	0.1mg/dL	≤0.05
Primary Author	**Drug LDL Difference**	**Control LDL Difference**	**LDL B/W Group P value**
Greenway [38]	-4.3mg/dL	0.3mg/dL	NS
Apovian [39]	-6.2mg/dL	-2.1mg/dL	≤0.01
Greenway [37]	-4.25mg/dL	-3.09mg/dL	NS
Primary Author	**Drug HDL Difference**	**Control HDL Difference**	**HDL B/W Group P value**
Greenway [38]	3.5mg/dL	1mg/dL	NS
Apovian [39]	-0.9mg/dL	3.6mg/dL	≤0.001
Greenway [37]	0.09mg/dL	0mg/dL	≤0.0001
Primary Author	**Drug TG Difference**	**Control TG Difference**	**TG B/W Group P value**
Greenway [38]	-43.6mg/dL	-15mg/dL	≤0.05
Apovian [39]	-11.65mg/dL	-0.564mg/dL	≤0.001
Greenway [37]	-14.79mg/dL	-3.45mg/dL	≤0.0001

Saxenda® (liraglutide)

We reviewed six studies for Saxenda® conducted by Wadden et al. [41-46] & (Table 10). Five out of six studies demonstrated statistically and clinically significant weight loss, and five out of six studies measuring waist circumference led to statistically significant values versus control six. Five out of five studies demonstrated statistically significant reductions in systolic blood pressure, five out of six studies demonstrated statistically significant reductions in fasting blood sugar, and all six studies demonstrated significant reductions in C-reactive protein. Two out of three Saxenda® studies demonstrated statistically significant differences in total and HDL cholesterol while one out of three studies demonstrated statistically significant differences in LDL cholesterol. Three out of three studies demonstrated statistically significant differences in triglycerides. Results are shown in Table 11.

Table 10: Selected studies for Saxenda®.

Primary Author	Year	Journal	Sample Size	Study Length
Wadden T.A.	2013	International Journal of Obesity	422 Participants	14 Months
Davies M.J.	2015	JAMA	846 Participants	14 Months
Pi-Sunyer X.	2015	New England Journal of Medicine	3662 Participants	14 Months
Blackman A.	2016	International Journal of Obesity	355 Participants	8 Months
Khoo J.	2017	Diabetes, Obesity and Metabolism	24 Participants	6.5 Months
Le Roux C.W.	2017	The Lancet	2210 Participants	14 Months

Table 11: Results of studies for Saxenda®.

Primary Author	Drug WT Difference	Control WT Difference	WT B/W Group P-value
Khoo [45]	-3.5kg	-3.5kg	NS
Wadden [41]	-6kg	-0.1kg	≤0.0001
Blackman [44]	-6.7kg	-1.9kg	≤0.0001
Davies [42]	-6kg	-2kg	≤0.001

Pi-Sunyer [43]	-8.4kg	-2.8kg	≤0.001
Le Roux [46]	-6.5kg	-2kg	≤0.0001
Primary Author	**Drug WC Difference**	**Control WC Difference**	**WC B/W Group P value**
Khoo [45]	-5.4cm	-4.5cm	NS
Wadden [41]	-4.7cm	-1.2cm	≤0.0001
Blackman [44]	-6.4cm	-3.1cm	≤0.0001
Davies [42]	-6.1cm	-2.7cm	≤0.001
Pi-Sunyer [43]	-8.2cm	-3.9cm	≤0.001
Le Roux [46]	-6.9cm	-3.4cm	≤0.0001
Primary Author	**Drug SBP Difference**	**Control SBP Difference**	**SBP B/W Group P value**
Wadden [41]	0.2mmHg	2.8mmHg	≤0.01
Blackman [44]	-3.4mmHg	0mmHg	≤0.001
Davies [42]	-2.8mmHg	-0.4mmHg	≤0.01
Pi-Sunyer [43]	-4.2mmHg	-1.5mmHg	≤0.001
Le Roux [46]	-3.2mmHg	-0.5mmHg	≤0.0001
Primary Author	**Drug DBP Difference**	**Control DBP Difference**	**DBP B/W Group P value**
Wadden [41]	1.4mmHg	1.2mmHg	NS
Blackman [44]	-0.7mmHg	-0.4mmHg	NS
Davies [42]	-0.9mmHg	-0.5mmHg	NS
Pi-Sunyer [43]	-2.6mmHg	-1.9mmHg	≤0.001
Le Roux [46]	-2.3mmHg	-1.9mmHg	NS
Primary Author	**D FBG Difference**	**C FBG Difference**	**FBG B/W Group P value**
Khoo [45]	-12.6mg/dL	-10.8mg/dL	NS
Wadden [41]	-9mg/dL	-3.6mg/dL	≤0.0001
Blackman [44]	-2.52mg/dL	-2.88mg/dL	≤0.0001
Davies [42]	-34.3mg/dL	-0.2mg/dL	≤0.001
Pi-Sunyer [43]	-7.1mg/dL	0.1mg/dL	≤0.001
Le Roux [46]	-6.66mg/dL	0.9mg/dL	≤0.0001
Primary Author	**D CRP (IQR) (mg/L) Difference**	**C CRP (IQR) (mg/L) Difference**	**CRP (IQR) (mg/L) B/W Group P value**
Khoo [45]	-0.03mg/dL	-0.98mg/dL	≤0.01
Wadden [41]	-2.113mg/dL	0.1155mg/dL	≤0.01
Blackman [44]	-2.226mg/dL	-0.809mg/dL	≤0.05
Davies [42]	-1.13934mg/dL	-0.3762mg/dL	≤0.001
Pi-Sunyer [43]	-1.47mg/dL	-0.3838mg/dL	≤0.001
Le Roux [46]	-3.87mg/dL	-1.16mg/dL	≤0.0001
Primary Author	**Drug TC Difference**	**Control TC Difference**	**TC B/W Group P value**
Wadden [41]	0.2mg/dL	0.3mg/dL	NS
Davies [42]	-1.46mg/dL	3.8mg/dL	≤0.01
Pi-Sunyer [43]	-3.1mg/dL	-1mg/dL	≤0.001
Primary Author	**Drug LDL Difference**	**Control LDL Difference**	**LDL B/W Group P value**
Wadden [41]	0.2mg/dL	0.3mg/dL	NS
Davies [42]	0.58mg/dL	5.02mg/dL	NS
Pi-Sunyer [43]	-3mg/dL	-1mg/dL	≤0.001

Primary Author	Drug HDL Difference	Control HDL Difference	HDL B/W Group P value
Wadden [41]	0.2mg/dL	0.1mg/dL	NS
Davies [42]	4.7mg/dL	1.93mg/dL	≤0.05
Pi-Sunyer [43]	2.3mg/dL	0.7mg/dL	≤0.001
Primary Author	**Drug TG Difference**	**Control TG Difference**	**TG B/W Group P value**
Wadden [41]	0mg/dL	0.1mg/dL	≤0.05
Davies [42]	-14.68mg/dL	0.41mg/dL	≤0.001
Pi-Sunyer [43]	-13.3mg/dL	-5.5mg/dL	≤0.001

Discussion

Twenty-four studies of the five FDA-approved weight loss drugs demonstrated clinically significant effects on weight loss with differing effects on both cardiovascular and glycemic markers/risk factors. Saxenda®, Belviq®, Contrave® and Qsymia® all positively affect fasting plasma glucose while Xenical® have no effect. Xenical®, Qsymia® and Contrave® demonstrated to have largely impacted cholesterol levels versus Belviq® and Saxenda® having minimal effects. Regarding systolic and diastolic blood pressure, Xenical®, Qsymia® and Saxenda® all showed positive effects compared to diet and exercise alone. According to Guideline for the Management of Overweight and Obesity in Adults, adjunctive pharmacotherapy should be considered for people who have either a BMI of 30 and over, or 27 and over with at least one comorbid conditions such as hypertension, dyslipidemia, type 2 diabetes or obstructive sleep apnea [14]. Even though it has been demonstrated that pharmacotherapy can enhance the likelihood of clinically meaningful weight loss and improve health, it is largely underutilized [17]. There is a potential role for pharmacist to be involved in primary care and serve as a liason between prescriber and weight management resources. Further research is needed to identify the cost effectiveness, most effective adjunctive behavioral treatments, the role of intermittent vs. continuous therapy as well as duration of treatment.

Conclusion

Underutilization of pharmacologic weight corrective therapies that have been statistically and clinically proven to be valuable tools in reducing obesity and its related risk factors [24]. Studies of the five FDA-approved drugs have demonstrated clinically significant effects on weight loss with differing effects on both cardiovascular and glycemic markers/risk factors.

Author Contributions

M.R. designed and directed the project; M.C. performed the experiments; M.H. wrote the manuscript with support from M.R. and M.C.

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