Pharmacotherapy in Pediatric Obesity: Current Evidence and Landscape

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Abstract

Purpose of review: Childhood obesity is escalating globally. Lifestyle and behavioral changes, which are the frequently used interventions in clinical practice lead to only modest improvements in children with established obesity. Bariatric surgery is currently the most effective obesity treatment but has very limited utilization in pediatric obesity and is preferentially used for children with worsening comorbidities. There exists a massive treatment gap for children suffering with obesity especially after the failure of lifestyle modifications. Pharmacotherapy which is an established management tool in adults is very infrequently used in children. Only two medications, Phentermine and Orlistat are approved by the Food and Drug Administration (FDA)for use in adolescent obesity. Herein, we discuss the current landscape and available literature on the use of anti-obesity pharmacotherapy in children.

Recent findings: There are emerging pediatric data about the efficacy of the many weight loss medications which are FDA approved in adults. Moreover, more clinical trials are underway on the rarer, intractable forms of obesity such as monogenic, syndromic and hypothalamic obesity.

Summary: Weight loss medications in children, like adults, have variable efficacy and similar side effect profile. Rigorous research and improved education of providers about weight loss medications may address the huge treatment gap in severe pediatric obesity.

Keywords

Pediatric obesity; Severe obesity; Pharmacotherapy; off label medications

Introduction

Pediatric obesity is an exponentially growing global public health concern. In the United States (US), the prevalence of obesity among children aged 2–19 years has more than tripled over the last four decades from 5% in 1978 to 18.5% in 2016[1]. Almost 1 in 5 youth is afflicted with obesity[2] and 9.5% of adolescents have severe obesity[3]. As the prevalence and severity of childhood obesity increases, associated acute and chronic comorbidities,

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previously considered to be adult diseases: type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease, metabolic syndrome, cardiovascular disease and obstructive sleep apnea, are more prevalent among children and commonly encountered in routine clinical practice. Children with obesity face significant social stigma predisposing them to serious negative consequences on their emotional and mental health and school performance[4,5]. Overall, obesity in childhood is a robust predictor of obesity in adulthood, and consequences may persist even if the excess childhood weight is lost[6,7]. Pediatric obesity has lifelong effects on patients, their families and health care systems and warrants appropriate treatment.

With these massive negative effects, it is essential to understand and utilize the treatment approaches available to treat the disease early in its course and to prevent worsening health. A stepwise approach is imperative to treat obesity in childhood. Lifestyle modifications including behavioral change, increased physical activity, and a balanced diet remain the first line and fundamental component of treatment throughout. Studies assessing these interventions have shown only modest persistent effects on BMI in pediatric patients. Separate Cochrane reviews found weak evidence that lifestyle modification dedicated to food, physical activity, and other behavior modifications reduce BMI in children and adolescents. Across 70 randomized controlled trials (RCT) in children with overweight and obesity aged 6 to 11 years, with duration of follow up ranging from six months to three years, BMI and weight decreased on average by 0.06 kg/m2 and 1.45 kg , respectively in the intervention groups compared with the control groups[8]. Similarly, across 44 RCTs in participants aged 12–17 years followed for six to twenty four months, the mean change in BMI z score was 0.13 units with a weight loss of 3.67 kg in lifestyle intervention group as compared with the controls[9].

There is a vast body of literature demonstrating the tremendous benefit of weight loss during early years[10,11]. Unfortunately, lifestyle modification alone is modestly effective in severe obesity. While bariatric surgery guidelines are available for pediatric patients with severe obesity, guidelines on the use of pharmacotherapy for patients who fail lifestyle modifications and are not candidates or are hesitant to get bariatric surgery are lacking[12]. Furthermore, the use of pharmacotherapy for pediatric obesity is currently limited and only two medications are Food and Drug Administration (FDA) approved. This leads to frequent off label use of medications which are approved in the adults only.

Henceforth, we provide a summary of literature of the FDA approved and non-approved medications (off label) used in pediatric obesity (Table 1). We also discuss the relative efficacy of some of the commonly used medications[13–17](Fig 1).

Discussion

Discussion of pharmacotherapy with the patient and family needs complete disclosure of the dearth of long-term data and the need of chronic usage (per adult data). This should be done under close monitoring with continued focus on lifestyle interventions and finding the lowest effective dose of medications.

A. FDA-Approved Anti-Obesity Medications in Pediatrics (Table1)

Only two medications, Orlistat and Phentermine are currently approved for weight loss in adolescents with obesity.

1. Orlistat ——Orlistat is the lone medication for long-term management of obesity for adolescents 12 years that is FDA approved. It inhibits the pancreatic and gastric lipase and decreases lipid absorption. The usual prescribed dose is 120 mg three times a day with meals. Most of the time its use is limited by the associated gastrointestinal side effects such as oily stools,abdominal pain, fecal urgency and incontinence, flatus as well as deficiency of fat-soluble vitamins[18,19]. Contraindications include chronic malabsorption, cholestasis and pregnancy[20].

2. Phentermine -—Phentermine is approved in the Unites States for adolescents>16 years for a short duration of up to 12 weeks. It reduces the reuptake of norepinephrine (NE) thereby stimulating the pro-opiomelanocortin (POMC) neurons in the hypothalamus[21] and also affects serotonin and dopamine reuptake , which in the pre-frontal cortex improves inhibitory control of appetite[22,23] (Fig 2) .The usual prescribed dosage is either 15 mg, 30 mg or 37.5 mg daily[24] . The most common side effects are irritability, insomnia, mood alteration, dry mouth, dizziness, tremor, headache, heart rate and blood pressure elevation and gastrointestinal side effects[14,25]. Contraindications include history of past or uncontrolled cardiovascular disease, hyperthyroidism, glaucoma and current use of monoamine oxidase inhibitors[22,26] (Table 1).

B. Non-FDA-Approved Anti-Obesity Medications in Pediatrics (Table1)

The lack of many FDA approved medications necessitates the off-label use of medications commonly used in adult obesity.

1. Topiramate—Topiramate is FDA approved for the treatment of epilepsy in 2 years of age and for migraine prophylaxis in 12 years of age and in combination with phentermine for obesity in 18 years of age. Topiramate blocks neuronal sodium channels, antagonizes glutamate receptors, inhibits carbonic anhydrase and is thought to suppress appetite via augmentation of the gamma-Aminobutyric acid (GABA)activity[15] (Fig 2). Side effects of Topiramate include reversible cognitive dysfunction, metabolic acidosis, nephrocalcinosis and paresthesia[15]. The recommended doses range from 25 mg to 100 mg. Topiramate is a teratogen and can cause orofacial defects in the fetus. It might also decrease the efficacy of oral contraceptives (less likely at the commonly used dose of <200 mg). Adolescents should be counseled on using other methods of contraception and serial pregnancy testing is recommended[22,26].

2. Phentermine/topiramate extended release (ER)—Phentermine/topiramate extended release (ER) combination is FDA approved for chronic weight management in adults. It was found to achieve greater weight loss than topiramate and phentermine monotherapy[27]. Side effects are similar to those seen when each compound is used alone and are dose dependent[28,29].

For monitoring, heart rate, blood pressure, electrolytes and creatinine should be assessed in the beginning of the treatment and periodically while on treatment, especially during dose adjustment[30].

3.   Bupropion/ Naltrexone -—Bupropion is a selective reuptake inhibitor of dopamine and noradrenaline (Fig 2), used in depression and smoking cessation treatment while Naltrexone is an opioid receptor antagonist used in opioid use disorder in adults[31]. The combination is approved for obesity treatment in adults. Bupropion/ Naltrexone carries a black box warning regarding increased suicidal risk and ideation in young adults and hence requires careful monitoring. Bupropion monotherapy for adolescents with depression was associated with side effects including irritability, dizziness, insomnia, headaches, nausea/ vomiting, decreased appetite, worsening anxiety, headaches, fatigue and tremor[32]. Usual side effects associated with Naltrexone are nausea, vomiting, headache, dizziness, insomnia[33–35] (Table 1).

4.   Metformin—Metformin is FDA approved for treatment of Type 2 Diabetes Mellitus > 10 years. Metformin inhibits hepatic gluconeogenesis (Fig 2) and enhances insulin-mediated glucose consumption in peripheral tissues (such as muscle and liver)[36]. Mechanism for its weight loss effects are largely unknown. Recommended dose ranges between 500 mg-2000 mg divided twice daily. Common adverse events are gastrointestinal in nature- bloating, flatus, diarrhea[16]. Metformin-associated lactic acidosis is rare but serious concern[37].

5.   Lis dexamphetamine—Lis dexamphetamine is a stimulant medication, FDA approved for children with ADHD   6 years and for binge eating disorder in adults. It decreases dopamine and noradrenaline reuptake in the nucleus accumbens, thus decreasing the hedonic/reward-based eating behaviors[38]. Increase in blood pressure and heart rate and worsening of psychiatric disorders may occur with its use[39–41] . In children and adolescents with cardiac abnormalities, sudden death has been reported[42,43].

6.   Glucagon-like peptide1 (GLP-1) analogues:

Exenatide/Dulaglutide/Liraglutide/Semaglutide: GLP-1 receptor agonists are incretins which enhance insulin secretion and increase satiety by slowing gastric emptying as well as by effect on the arcuate nucleus of the hypothalamus, limbic/reward system in amygdala and the cortex[44–46](Fig 2) . Adverse effects are primarily gastrointestinal-nausea, vomiting, and diarrhea[47–49]. Liraglutide is contraindicated in patients who have a personal or family history of medullary thyroid carcinoma or type 2 multiple endocrine neoplasia[50].

The different GLP-1 agonists differ in their duration of action and efficacy to the receptors[51]. Liraglutide, due its slower degradation allows for once daily dosing and is FDA approved for obesity treatment in adults and T2DM in both adults and adolescents[52]. The initial recommended dose is 0.6 mg injected subcutaneously and gradually augmented in increments of 0.6 mg weekly to the maximum dose of 3.0 mg. This slow increase helps to minimize the associated gastrointestinal side effects[52].

Semaglutide-: Semaglutide the newest GLP-1 agonist which demonstrated promising results in adults with obesity. It is a long acting GLP-1 receptor agonist with decreased degradation

by dipeptidyl peptidase (DPP-4), allowing once weekly dosing[53]. There are ongoing clinical trials with weekly Semaglutide in adolescents with obesity (NCT04102189).

C. Pharmacotherapy for syndromic obesity

Syndromic obesity is characterized by a wide variety of features involving various organ systems such as intellectual disability, developmental delay, dysmorphic features, retinal changes and deafness. Obesity is typically early onset in nature and associated with hyperphagia. Over 25 syndromic forms of obesity have been identified.[54,55]. Prader-Willi syndrome (PWS) is the most common of these[55]. Others includes Bardet-Biedl syndrome (BBS), Alström syndrome, Albright hereditary osteodystrophy (pseudohypoparathyroidism type 1A) and more. Details of syndromic obesity are beyond the scope of this review.

Unfortunately, obesity management in these syndromes is challenging. Lifestyle based therapy are crucial in order to drop the risk of obesity comorbidities. Currently, there are no approved anti-obesity pharmacotherapy available for syndromic obesity, but studies are ongoing. GLP-1 agonists may have some beneficial role in PWS, but data are evolving. A small, single blinded crossover study in patients with PWS receiving a single 10-μg exenatide injection or placebo demonstrated increased satiety and lowered glucose level[56] . One year of exenatide and liraglutide use in young females with PWS demonstrated marked reduction in BMI as well as food consumption and decreased ghrelin levels[33,57,58]. On the other hand, in a six-month, open-label, nonrandomized longitudinal study of patients with PWS receiving exenatide, weight and adiposity were unaffected even though hunger scores and hemoglobin A1c reduced after treatment.[59]

Oxytocin (OXT) is another compound under investigation. Oxytocin is produced by the hypothalamus and regulates food consumption via hedonic and homeostatic pathways and is administered intranasally. In adults, oxytocin decreases the total caloric and fat intake while increasing fat utilization and causing weight loss.[60–62] In children, it has been mainly studied in PWS subjects has shown promising effects on food related behaviors and reduction in appetite drive[63–65].

D. Pharmacotherapy for monogenic obesity

Monogenic obesity is caused by single-gene defects in which early onset obesity and hyperphagia are the key characteristics. Loss-of-function mutations in genes involved in the leptin-melanocortin pathway (pathway of homeostatic energy regulation) (Fig 2), are implicated in rare forms of monogenic obesity[36]. Metreleptin, the recombinant form of leptin produced extreme weight loss, significant improvement in hyperphagia , decrease in hunger scores and resolution of metabolic consequences when administered to patients with congenital leptin deficiency[66,67].

Setmelanotide (RM-493), a synthetic melanocortin –4-receptor (MC4R) agonist (Fig 2), is being tested for the treatment of monogenic obesity. In a small open-label study in individuals with leptin receptor (LepR) deficiency and POMC deficiency, Setmelanotide led to reductions in body weight and decreased hunger scores[68,69]. Described adverse events included dry mouth, localized skin induration at injection sites and darkening of skin nevi[68].

E. Pharmacotherapy for Hypothalamic Obesity (HO)

Hypothalamic Obesity is another severe form of obesity, mostly seen after craniopharyngioma resection or with other diseases affecting the medial hypothalamic region. It is characterized by exponential weight gain leading to severe obesity, voracious appetite and poor satiety, decreased resting energy expenditure and fatigue. Standardized and effective treatments are lacking for HO.

The efficacy of improvement of satiety by GLP-1 agonists is being evaluated in HO[70]. In a small prospective study of adults with HO, treated with exenatide for 52 weeks, subjects were noted to have decreased food intake and 75% of them had stable or decreasing trends in weight[71]. Several case reports and small studies also support the efficacy of Liraglutide[72,73]. A retrospective study of exenatide or liraglutide treatment in HO patients for up to 51 months, demonstrated a reduced BMI from 37.6 kg/m2 to 33.4 kg/m2[74].

Dextroamphetamine, an adrenergic agonist may mitigate weight gain through central anorexigenic effects. A case series of 7 adolescent and young adult patients with HO treated with dextroamphetamine showed a reduction of 0.18 units in BMI z-score during the first year of treatment. However, the weight loss effects of treatment during the second year were heterogenous ,where some patients continued to lose weight and others showed significant increase in the BMI z score , making the long-term efficacy of this treatment suspicious.[75]

Diazoxide and Metformin in combination has also been evaluated in a small prospective study for 6 months in pediatric patients with HO. The decrease in the BMI standard deviation score (SDS) was significantly greater with treatment as compared with that of the pre-study period with lifestyle intervention alone (-0.04 ± 0.15 versus $+0.11 \pm 0.08$)[76]. In another RCT of pediatric patients randomized to either diazoxide or placebo for 2 months, BMI was not significantly different between the groups[77]. Hence larger studies with longer follow up are required to establish the true efficacy of these medications.

Conclusion

Obesity, especially severe obesity, in the pediatric population is increasing. Large studies have demonstrated that lifestyle interventions alone only have modest benefits in reversing the trends of severe obesity. While lifestyle modification and physical activity remain the cornerstone for treating and managing obesity, pharmacologic interventions should be considered to slow the weight gain and decrease the risk of complications, particularly in children who fail to lose weight on lifestyle modifications and demonstrate new or worsening comorbidities. While there are many anti-obesity medications approved for adults, only one medication is approved for long-term use in the pediatric population and another one for short term use only. Although there are medications in the pipeline, further high-quality research in pediatric anti-obesity pharmacotherapy with subsequent FDA approval of more medications is critical to address this huge treatment gap.

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KEY POINTS:

Severe obesity is escalating, and lifestyle-based therapies have modest effects in changing the trajectory of the disease.

Treatment of obesity needs additional and more efficacious treatment options which should be tailored based on the age of the patient, severity of disease and associated comorbidities.

Anti-obesity pharmacotherapy should be utilized in patients who have failed attempts to weight loss after lifestyle modifications.

Syndromic, monogenic and hypothalamic obesity are other severe forms of obesity which remain recalcitrant to standard treatment options.
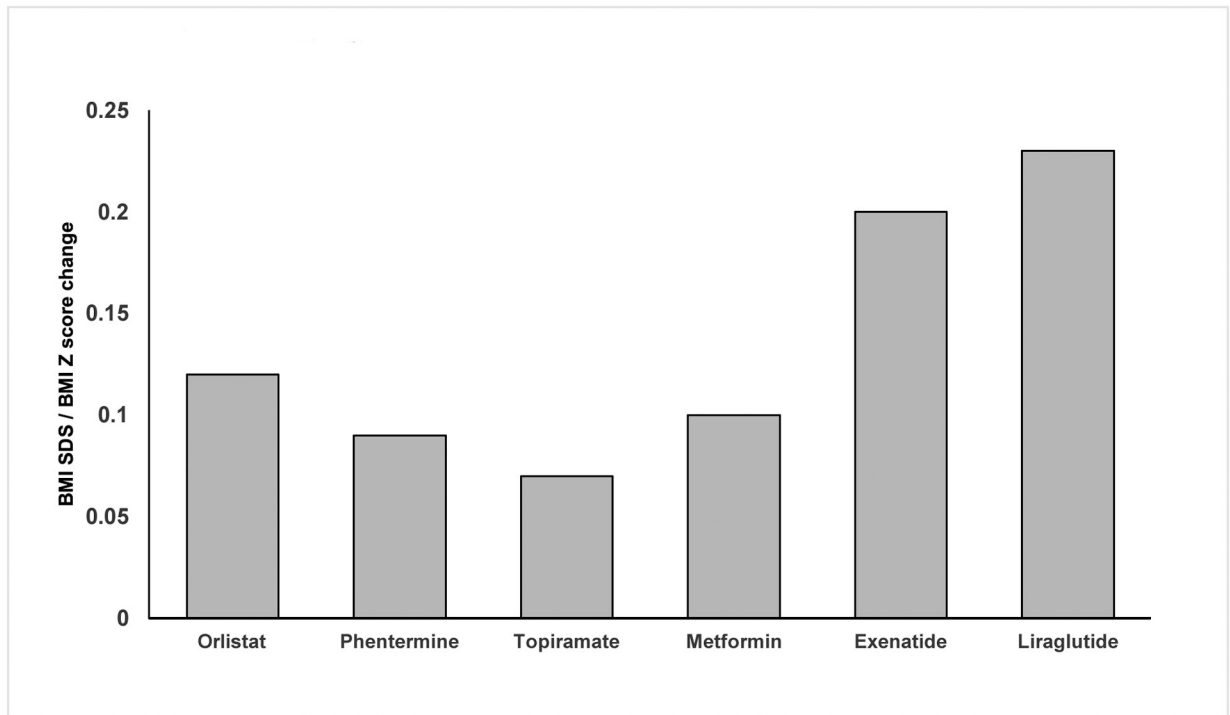
Fig 1: BMI SDS/BMI Z score change by weight loss medication
A BMI SDS change from representative controlled trials is reported for Orlistat, Metformin, Exenatide, Liraglutide. A BMI Z score change from representative studies is reported for Phentermine, Topiramate.[10–14]
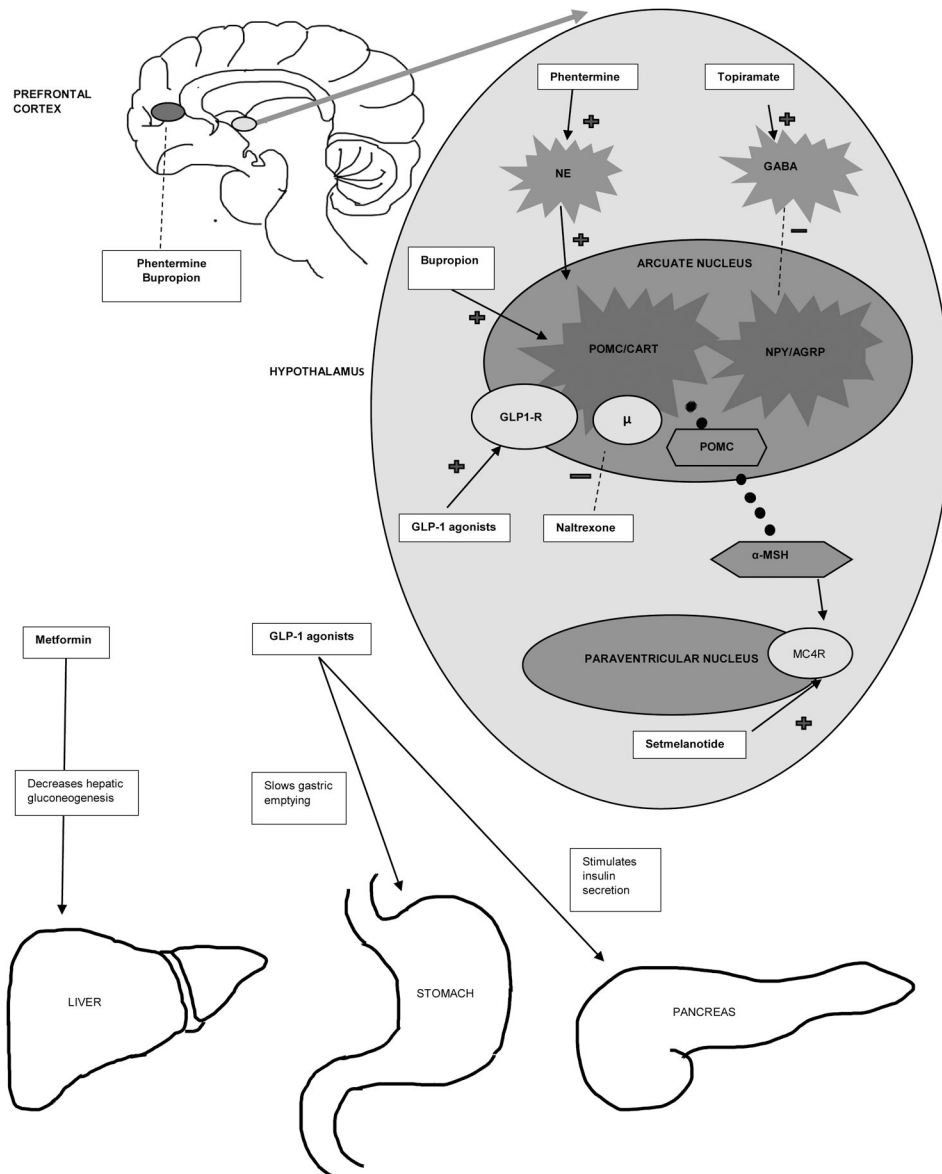
Figure 2: Sites and mechanism of action of various anti-obesity medications. (Original representation)

The hypothalamic region of the brain is the primary site of action of many anti-obesity medications. The arcuate nucleus of the hypothalamus harbors the proopiomelanocortin (POMC)/cocaine and amphetamine regulated transcript (CART) neurons as well as the agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons. Activation of POMC/CART results in decrease food intake and increased resting energy expenditure (REE)and activation of AgRP/NPY results in is orexigenic effects. The main product of POMC/CART neuron activation is POMC. POMC undergoes proteolytic cleavage to produce many active peptides. Alpha melanocyte stimulating hormone (α-MSH), a product of POMC acts as a ligand to Melanocortin 4 receptor (MC4R) located on the neurons of the paraventricular nucleus of the hypothalamus. Activation of the melanocortin pathway leads to increased

REE and decrease in food intake. Various medications exert the weight loss effect by central and/or peripheral mechanisms as illustrated in the figure.

NE: Nor epinephrine; GABA, gamma-Aminobutyric acid; GLP-1, glucagon-like peptide

Table 1:

Summary of medications used for the treatment of pediatric obesity.

Medication	Mechanism	Side effects	Contraindications	Efficacy from Pediatric data (different measures of weight change reported)
Orlistat[13,18,19,78]	• Inhibits pancreatic and gastric lipase • Decreases lipid absorption	GI symptoms -abdominal pain, oily stools and spotting, fecal urgency & incontinence, flatus, fat soluble vitamin deficiency	Chronic malabsorption, cholestasis, pregnancy	−2.61-kg placebo-subtracted weight loss after 1 year of treatment.
Phentermine[14,22,28]	• Norepinephrine reuptake inhibitor • Inhibits hypothalamic catecholamine release	Irritability, insomnia, dry mouth, dizziness, tremor, headache, HR and BP elevation. GI symptoms- abdominal pain, diarrhea, constipation, nausea	Cardiovascular disease, hyperthyroidism, glaucoma, co-use of monoamine oxidase inhibitors	4.1% reduction in BMI and 3.2 kg reduction in weight at 6-months with phentermine and lifestyle modification compared to lifestyle modification only
*Topiramate[15,26,29,79]	• Augments the GABA (A) activity • Blocks neuronal Na channels • Antagonizes glutamate receptors • Weakly inhibits carbonic anhydrase	Cognitive dysfunction, paresthesia, nephrolithiasis, metabolic acidosis	Pregnancy (teratogen), acute myopia and secondary angleclosure glaucoma	2 – 4.9% BMI reduction with 75 mg of topiramate for 6 months
*Bupropion/ Naltrexone[24,32,33,80]	• Bupropion selectively inhibits reuptake of dopamine and noradrenaline • Naltrexone is an opioid receptor	Headache, dizziness, vomiting, constipation, dry mouth. irritability, dizziness, insomnia, headaches, anxiety, fatigue and tremor	A black box warning of increased suicidal risk and ideation in young adults	Data is not available for < 18 years
*Metformin[26,36,78]	• Biguanide, interferes with protein kinase signaling, thus suppressing glucose production in the liver and its absorption from the intestine • Increase glucose uptake in the periphery	Mostly GI symptoms- bloating, flatus, diarrhea, usually well tolerated	Severe Hepatic/Renal Disease	BMI Z score reduction of 0.1 and BMI reduction of 0.86 compared to placebo
*Lis dexamphetamine[40,41]	• Dopamine agonist • CNS stimulator	Diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, abdominal pain, vomiting, HR and BP elevation	Cardiovascular diseases Psychiatric adverse reactions Serotonin syndrome with use of serotonergic agent.	0.24–0.51-point reduction in BMI z score (dose dependent)
*GLP-1 agonists[17,26,47–49,55,57–59,81,82] Exenatide Liraglutide	• Enhance insulin secretion • Slowing gastric emptying • Act on the hypothalamus, limbic/reward system and cortex	GI symptoms- nausea, vomiting, diarrhea Hypoglycemia risk in those on insulinotropic medications A small risk of cholelithiasis and pancreatitis	Pregnancy, personal or family history of medullary thyroid carcinoma or type 2 multiple endocrine neoplasia	Absolute BMI reduction of 3.42% with exenatide for 3–6 months BMI SDS reduction of 0.23 with 56 weeks of Liraglutide vs placebo

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GI, gastrointestinal; HR, heart rate; BP, blood pressure; BMI, body mass index; GABA, gamma-Aminobutyric acid; CNS, central nervous system; GLP-1, glucagon-like peptide 1; SDS, standard deviation score;

*
Non-FDA- approved medications for indication of weight loss (off label use)