Exploring Current Pharmacological Treatments for Genetic Obesity with Setmelanotide in Focus: A Narrative Review

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ABSTRACT

Genetics play a crucial role in early childhood obesity which is a multifactorial disease that is highly prevalent and poses a significant challenge to public health.

Objective: The objective of this review was to evaluate and summarize the research on the efficacy and limitations of setmelanotide for the treatment of pediatric obesity of genetic factors.
Methodology: Electronic databases were explored with Boolean operator mixed keywords like pediatric obesity, genetic obesity, pharmacotherapy, and setmelanotide. The main focus was on setmelanotide approaches on pediatric studies published in English from 2018 to 2023.

Results: Setmelanotide a melanocortin-4 receptor, is an approved treatment and well tolerated among pediatric patients aged ≥ 6 years and shown to be effective in at least 10% reduction in body weight within a year of treatment. This review comprises a narrative review on setmelanotide and a tabular summary of the current available evidence for the management of pediatric obesity in terms of medical options.

Conclusion: Research into adult obesity has established pharmacological novel therapies, which have been approved and established in clinical practice; however, the research and implementation of such therapies in pediatric populations have been lagging behind. Further research is justified, to address the huge treatment gap in severe pediatric obesity.

Keywords: Pediatric obesity, Pharmacotherapy, off label medications, genetic obesity, setmelanotide, endocrinology, pediatrics, pharmacotherapy

INTRODUCTION

According to the Endocrine Society Practice guidelines for pediatric society, a body mass index (BMI) ≥ 95th percentile, extreme obesity as BMI ≥120% of the 95th percentile or ≥35 kg/m^2 is defined as childhood obesity[1]. Childhood obesity is on high prevalence and is a rapidly growing problem in Saudi Arabia and that children are at risk of becoming overweight and obese with age [2,3],and it has been on the rise than adult obesity[4]. The social stigma of obesity is a societal burden[5, 6]which needs to be addressed at the earliest for the overall wellbeing of the affected and their family as well. Thus, an early diagnosis and prompt clinical management of pediatric obesity are very critical. Genetic obesity should be considered if a patient <5 years presents with extreme obesity and should be indicative for the subsequent genetic evaluation to identify underlying molecular genetic defect[7].

Though its assumed and accepted that most pediatric obesity is commonly due to the consumption of high fat and energy foods, the role of genetic variants in obesity pathogenesis cannot be undermined. Up to 5 % of extreme pediatric obesity are associated with genetic disorders, as per the recent studies [8, 9].

Comorbidities like dyslipidemia, hypertension, fatty liver disease and psychosocial complications are becoming increasingly prevalent within the obese pediatric populations [10,11]. Current treatment guidelines focus mainly on intervention with modifications of lifestyle practices and pharmacotherapy[12,13]. Patients who are resistant to such interventions were reserved for surgical options. Many novel pharmacological practices has been established and approved for adult obesity treatments [14, 15], but such interventions are yet to be validated in pediatric populations. The relative lack of interventional research in pediatric obesity in comparison to the adult obese population needs to be highlighted and thus calls for newer therapies to be trialed for the treatment options for childhood obesity.

This review comprises a narrative review on setmelanotide and a tabular summary the current available evidence for the management of pediatric obesity in terms of medical options. Summarized in Table 1 is their mechanism of action, Food and Drug Administration (FDA) approval status, recommended frequency and route, adverse effects and safety profiles of the medicines from clinical trial data.

MATERIALS AND METHODS

PubMed was used to identify literature for this review with Boolean operator mixed keywords like pediatric obesity, genetic obesity, pharmacotherapy, setmelanotide. The main focus was on setmelanotide approaches on pediatric studies published in English from 2018 to 2023. Editorials, other review, commentaries, letters to editors were

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excluded. The references of selected articles were also analyzed to ensure additional information was obtained where appropriate.

The search engine PubMed was used to identify literature for this review. Keywords used included childhood obesity, setmelanotide, pharmacotherapy, metformin, orlistat, glucagon-like peptide 1, sibutramine, topiramate, phentermine, lorcaserin, lisdexamfetamine, naltrexone, bupropion, fluoxetine, zonisamide, metreleptin. Pediatric studies with patients less than eighteen years of age is the focus of interest in this review.

CURRENT PHARMACOLOGICAL TREATMENTS: MEDICATIONS APPROVED FOR PEDIATRIC OBESITY

Off label medications like Metformin has been often used in the pediatric obesity treatment. Despite the minimal efficiency these medications were uses due to its ease of availability and relatively low-risk safety[16]. Many medications like rimonabant, lorcaserin, and sibutramine, approved in adults and used off-label in the pediatric population have been discontinued because of significant safety concerns among the pediatric population[17].

Setmelanotide: A melanocortin receptor MC4R agonist, setmelanotide is a cyclized octapeptide which was introduced in 2016[18], acts by mimicking the pro-opiomelanocortin (POMC) derivative α-MSH that could result in reducing food intake and substantial weight loss [19,20].

It is one of multiple MC4R agonists that have been studied as potential anti-obesity medication. Setmelanotide has not been reported to increase heart rate making while other MC4R agonists have reports which make them unacceptable in clinical care[21,22]. In a obese nonhuman model, setmelanotide produced persistent weight loss (–13.5%) over 8 weeks[23] Clinical trials show that patients with POMC has been shown to have beneficial effects from setmelanotide[24]. Most genes implicated in monogenic obesity are involved in MC4R pathway, setmelanotide has been researched in patients with central leptin-melanocortin pathway defects in like leptin receptor deficiency and MC4R deficiency[25.26].

Setmelanotide by infusion over 28 days was used for the treatment of obese individual for complete or partial loss of function mutations in MC4R in a phase 1b study and was shown to be effective with no increases in heart rate or blood pressure[27] . The frequent side effect associated with setmelanotide reported was hyperpigmentation or darkening of the skin[27,28].

A recent single-arm, open-label, multicentre, phase 3 trial study[29] across seven countries in the patients with POMC or leptin receptor (LEPR) deficiency who received either setmelanotide or placebo for a year, reported that 80% participants in the POMC group and 45% participants

Table1: Summary of medications used in the clinical practice for managing obesity pediatric and adolescent (>10 years) populations

Medication	Mechanism of action	Licensed/approved				Dose, Frequency and Route	Adverse effects	Contraindications and warnings
		FDA	EMA	Pediatric	Adolescent			
Setmelanotide[41]	Melanocortin-4 receptor (MC4R) agonist	√	√	√ >6 years for POMC, PCSK1, or LEPR deficiency in patients	√ for POMC, PCSK1, or LEPR deficiency in patients	N/A OD SC	Darkening of the skin, injection site reactions, nausea, headache, diarrhea, stomach pain, vomiting, depression, non-sexual erection in male.	History of depression or suicidal ideation
Orlistat (tetrahydrolipstatin) [42, 43, 44]	Lipase inhibitor, blocks fat absorption	√	×	×	√ children ≥12 years	120 mg TDS PO	Anxiety, Steatorrhea, fecal incontinence, and frequent bowel movements	Pregnancy, patients with chronic malabsorption or cholestasis. To be used in caution when prescribing to patients with history of hyperoxaluria
Liraglutide(Saxenda) [45,46]	GLP-1 agonist	√	√	√	≥ 12 years with BMI ≥ 95th percentile for age and sex and weight	0.6–3 mg OD SC	Gastrointestinal symptoms, headache, dyspepsia, fatigue, dizziness, tachycardia, renal impairment	Renal failure, Family history of thyroid carcinoma/multiple endocrine neoplasia risk of thyroid C-cell tumors. Individuals with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Active gallbladder disease or pancreatitis Depression or suicidal thoughts

Metreleptin [47,48]	Recombinant analogue of leptin	√	√	√ approval for the use of metreleptin for rare lipodystrophy	√ approval for the use of metreleptin for rare lipodystrophy	Up to 0.13 mg/kg OD SC	Fatigue, hypoglycemia, , T-cell lymphoma (uncommon) Hypersensitivity, including urticaria and generalized rash	Presence of anti-metreleptin antibodies, Severe infection and/or worsening metabolic control
Semaglutide(Wegovy; Novo Nordisk) [49,50,51]	GLP-1 agonist	√	√	×	√ >12 years	0.25 mg (max 1 mg) (adults) Weekly SC	Pancreatitis, retinopathy, hypoglycemia, acute kidney injury, hypersensitivity Reactions, gastrointestinal disturbance.	Medullary thyroid carcinoma, MEN2
Exenatide(Bydureon)[52,53]	GLP-1 agonist	√	×	×	√ 10-17 years with type 2 diabetes	5–10 mcg (adults) BD SC	Gastrointestinal symptoms, hypoglycemia, pancreatitis, renal failure	Renal failure, Family history of thyroid carcinoma/MEN2
Metformin[54,56]	Inhibition of gluconeogenesis, improves insulin sensitivity	√	×	√	√ 10-17 years with type 2 diabetes	200–500 mg initially (max 2 g/day) BD PO	Gastrointestinal disorders (abdominal pain, reduced appetite, diarrhea, nausea, altered taste, vomiting)	Metabolic acidosis
Topiramate[57,58]	Carbonic anhydrase inhibitor, appetite suppression through potential GABA augmentation	√	Topiramate	×	√ ≥ 12 years with BMI ≥ 95th percentile for age and sex and weight	N/A OD or BD PO	Paresthesia, difficulty concentrating, mood changes and memory issues	Porphyria, pregnancy
Phentermine(Qsymia) [59,60,61]	• Norepinephrine reuptake inhibitor • Inhibits hypothalamic catecholamine release	√	×	×	≥ 12 years with a BMI> 95th percentile for age and sex	N/A OD PO	Tachycardia, gastrointestinal disturbances, dizziness, insomnia and dry mouth, euphoria, dysphoria, tremor, headache, psychosis, and changes in libido Rare cases of primary pulmonary hypertension, ischemic events.	Hypersensitivity to sympathomimetic amines, history of cardiovascular disease, glaucoma, agitated states, hyperthyroidism , history of drug abuse, pregnancy and breastfeeding

Note: N/A, dosage recommendations for clinical use not available.
BWFI, bacteriostatic water for injection; BMI, body mass index; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; GLP-1R, glucagon-like peptide-1 receptor; OTC, over the counter; WFI, water for injection.*a*Saxenda is currently the only formulation of liraglutide that is FDA approved for treatment of pediatric obesity.BD, twice daily; CV, cardiovascular; EMA, European Medicines Agency; FDA, Food and Drug Administration; LEPR, leptin receptor; OD, once daily; PCSK1, proprotein convertase subtilisin/kexin type 1; PO, oral; POMC, proopiomelanocortin; SC, subcutaneous; T2DM, type 2 diabetes mellitus; TDS, three times a day, multiple endocrine neoplasia syndrome type 2 (**MEN** 2)

in the LEPR group achieved at least 10% weight loss. Hunger scores were also significantly reduced for both POMC and LEPR deficiency groups[30,31]. Setmelanotide is indicated for chronic weight management in patients aged 6 years or over with confirmed POMC, proprotein convertase subtilisin/kexin type 1 and LEPR deficiency[32].

Patients with Bardet Biedl syndrome has been shown to respond well to setmelotide[33] with hunger reduction and mean weight loss at 1 year of –16.3%. Given the global prevalence of obesity, it can be noticed that setmelanotide is being tested in rare genetic disorders like Alström syndrome SRC1, SH2B1, and MC4R deficiency[34], and Smith-Magenis syndrome in a basket Phase 2 trial[35]. Efforts to identify other patients with other genetic obesity syndromes that might respond to setmelanotide is being expanded.

Overall, the efficacy and safety profile of setmelanotide supports its potential long-term use as a treatment for early-onset severe obesity and hyperphagia caused by POMC or LEPR deficiency[36,37]. With the support of these findings, setmelanotide in 2020 got approved from the U.S. Food and Drug Administration and European Medicines Agency (EMA) in July 2021 for the management of obesity in adult and children aged 6 years and older with monogenic obesity due to POMC, PCSK1, or leptin receptor deficiency[38,39].

Regulatory approval of setmelanotide is limited only for patients with proven genetic defects in the leptin-melanocortin pathway. It is usually associated with severe childhood obesity and hyperphagia and may be associated with various other endocrinopathies, e.g., adrenocorticotropic hormone deficiency, hypothyroidism, hypogonadism, hypopigmentation, hypoglycemia, and others[40]. Though a rare occurrence these genetic, conditions present huge challenges for health care providers, patients and families. This should support the clinicians requirement to increase genetic testing for patients with a history of severe early-onset obesity. Setmelanotide thus should have a place of appreciation in the pediatric obesity clinic in understanding the underpinnings of obesity and an increase in genetic screening to identify a subset of pediatric obese patients. Thus despite of the side effect of a skin pigmentation, setmelanotide is likely to be the optimal choice of treatment for pediatric obese patients with proven genetic defects in the melanocortin pathway.

Table 1 is illustrative and descriptive of the comparison between the current anti-obesity medications used in the clinical practice for managing obesity pediatric and adolescent (>10 years) populations.

CONCLUSION

Providing the best options in the clinical practice of pediatric obesity medicine has been a struggle for providers as well as the patients .Obesity in children has a high risk of persisting in to adolescence and adulthood, leading to chronic comorbidities. In comparison to researches undertaken in the adult obesity treatments, there is a critical lack of potential clinical trials undertaken in childhood obesity treatments. It is of utmost clinical importance that there is availability of effective anti-obesity medications with different mechanisms of action which can be well tolerated by the patients. The key focus should be to shift the focus from treating the comorbidities, but to identify the root cause of these comorbidities—obesity and provide optimal treatment eradicating the cause.

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REFERENCES

1. Kim JH. Overview of pediatric obesity: diagnosis, epidemiology, and significance. J Korean Med Assoc 2021;64(6):401-9.
2. Habbab RM, Bhutta ZA. Prevalence and social determinants of overweight and obesity in adolescents in Saudi Arabia: a systematic review. Clinical Obesity 2020;10(6):e12400.
3. Al-Hussaini A, Bashir MS, Khormi M, et al. Overweight and obesity among Saudi children and adolescents: Where do we stand today?. Saudi J Gastroenterol 2019;25(4):229.
4. Wiss DA, Brewerton TD. Adverse childhood experiences and adult obesity: a systematic review of plausible mechanisms and meta-analysis of cross-sectional studies. Physiol Behav 2020;223:112964.
5. Alaqeel AA. Pediatric diabetes in Saudi Arabia: Challenges and potential solutions. A review article. Int J Pediatr Adolesc Med 2019;6(4):125-30.
6. Ghamri RA, Hegazy AA, Azizkhan AZ, et al. High blood pressure in children attending pediatric clinic at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. J Family Community Med 2019;26(3):193.
7. Sohn YB. Genetic obesity: an update with emerging therapeutic approaches. Ann Pediatr Endocrinol Metab 2022;27(3):169-75.
8. Morales Camacho WJ, Molina Díaz JM, et al. Childhood obesity: Aetiology, comorbidities, and treatment. Diabetes Metab Res Rev 2019;35(8):e3203.
9. Haqq AM, Kebbe M, Tan Q, et al. Complexity and stigma of pediatric obesity. Child Obes 2021;17(4):229-40.
10. Utkirzhonovna SN. Main risk factors for overweight and obesity in young people. Eurasian medical research Periodical 2022;7:141-6.
11. Calcaterra V, Regalbuto C, Porri D, et al. Inflammation in obesity-related complications in children: The protective effect of diet and its potential role as a therapeutic agent. Biomolecules 2020;10(9):1324.
12. Srivastava G, Fox CK, Kelly AS, et al. Clinical considerations regarding the use of obesity pharmacotherapy in adolescents with obesity. Obesity 2019;27(2):190-204.
13. Czepiel KS, Perez NP, Campoverde Reyes KJ, et al. Pharmacotherapy for the treatment of overweight and obesity in children, adolescents, and young adults in a large health system in the US. Frontiers in Endocrinology 2020;11:290.
14. Khalil H, Ellwood L, Lord H, et al. Pharmacological treatment for obesity in adults: an umbrella review. Ann Pharmacother 2020;54(7):691-705.
15. May M, Schindler C, Engeli S. Modern pharmacological treatment of obese patients. Ther Adv Endocrinol Metab 2020;2042018819897527.
16. Ford JL, Gerhart JG, Edginton AN, et al. Physiologically based pharmacokinetic modeling of metformin in children and adolescents with obesity. J Clin Pharmacol 2022;62(8):960-9.
17. Tak YJ, Lee SY. Long-term efficacy and safety of anti-obesity treatment: where do we stand?. Curr Obes Rep 2021;10(1):14-30.
18. Yeo GS, Chao DH, Siegert AM, et al. The melanocortin pathway and energy homeostasis: From discovery to obesity therapy. Mol Metab 2021;48:101206.
19. Kühnen P, Krude H, Biebermann H. Melanocortin-4 receptor signalling: importance for weight regulation and obesity treatment. Trends Mol Med 2019;25(2):136-48.
20. Markham A. Setmelanotide: first approval. Drugs 2021;81:397-403.
21. Ryan DH. Setmelanotide: what does it mean for clinical care of patients with obesity?. The Lancet Diabetes & Endocrinology. 2020;8(12):933-5.
22. Cignarella A, Busetto L, Vettor R. Pharmacotherapy of obesity: an update. Pharmacol Res 2021;169:105649.
23. Bischof JM, Van Der Ploeg LH, Colmers WF, et al. Magel2-null mice are hyper-responsive to setmelanotide, a melanocortin 4 receptor agonist. Br J Pharmacol 2016;173(17):2614-21.
24. Low MJ. New hormone treatment for obesity caused by POMC-deficiency. Nat Rev Endocrinol 2016;12(11):627-8.

25. Sohn YB. Genetic obesity: an update with emerging therapeutic approaches. Ann Pediatr Endocrinol Metab 2022;27(3):169-75.
26. Collet TH, Dubern B, Mokrosinski J, et al. Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency. Mol Metab 2017;6(10):1321-9.
27. Kanti V, Puder L, Jahnke I, et al. A Melanocortin-4 receptor agonist induces skin and hair pigmentation in patients with monogenic mutations in the leptin-melanocortin pathway. Skin Pharmacol Physiol 2021;34(6):307-16.
28. Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol 2020;8(12):960-70.
29. Kühnen P, Wabitsch M, von Schnurbein J, et al. Quality of life outcomes in two phase 3 trials of setmelanotide in patients with obesity due to LEPR or POMC deficiency. Orphanet J Rare Dis 2022;17(1):1-1.
30. Trapp CM, Censani M. Setmelanotide: a promising advancement for pediatric patients with rare forms of genetic obesity. Curr Opin Endocrinol Diabetes Obes 2023;30(2):136-40.
31. Ben-Ami M, Eirini Kostopoulou MD, Martos-Moreno G, et al. Effects of Setmelanotide on Obesity, Hunger, and Safety in SRC1 Insufficiency: A Phase 2 Trial. Obes 2021;29:91-2.
32. Cuda S, Censani M. Progress in pediatric obesity: new and advanced therapies. Curr Opin Pediatr 2022;34(4):407-13.
33. Tauber M. Setmelanotide for controlling weight and hunger in Bardet-Biedl syndrome. Lancet Diabetes Endocrinol 2022;10(12):829-30.
34. Clément K, Mosbah H, Poitou C. Rare genetic forms of obesity: From gene to therapy. Physiol Behav 2020;227:113134.
35. Poitou C, Mosbah H, Clément K. Mechanisms in endocrinology: update on treatments for patients with genetic obesity. European J Endocrinol 2020;183(5):R149-66.
36. Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. Lancet Diabetes Endocrinol 2020 ;8(12):960-70.
37. Haws R, Brady S, Davis E, et al. Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome. Diabetes Obes Metab 2020;22(11):2133-40.
38. Apperley LJ, Blackburn J, Erlandson-Parry K, et al. Childhood obesity: A review of current and future management options. Clin Endocrinol 2022;96(3):288-301.
39. Srivastava G, Fox CK, Kelly AS, et al. Clinical considerations regarding the use of obesity pharmacotherapy in adolescents with obesity. Obes 2019;27(2):190-204.
40. Ryan DH. Drugs for treating obesity. From Obesity to Diabetes 2021:387-414.
41. Stagi S, Bianconi M, Sammarco MA, et al. New thoughts on pediatric genetic obesity: pathogenesis, clinical characteristics and treatment approach. Adiposity-Omics and Molecular Understanding. 2017 Mar 22.
42. Kim BY, Kang SM, Kang JH, et al. Current long-term pharmacotherapies for the management of obesity. J Obes Metabol Synd 2020;29(2):99-109.
43. Bansal AB, Al Khalili Y. Orlistat. InStatPearls [Internet] 2022 Jul 21. StatPearls Publishing.
44. Brown SA, Izzy M, Watt KD. Pharmacotherapy for weight loss in cirrhosis and liver transplantation: translating the data and underused potential. Hepatol. 2021;73(5):2051-62.
45. Age FA, Contraindications I. FDA-Approved Drugs to Treat Overweight and Obesity.
46. Raman V, Gupta A, Ashraf AP, et al. Pharmacologic weight management in the era of adolescent obesity. J Clin Endocrinol Metabol 2022;107(10):2716-28.
47. Bays HE, Fitch A, Christensen S, et al. Anti-obesity medications and investigational agents: an obesity medicine association (OMA) clinical practice statement (CPS) 2022. Obes Pillars 2022;2:100018.
48. Calcaterra V, Magenes VC, Rossi V, et al. Lipodystrophies in non-insulin-dependent children: Treatment options and results from recombinant human leptin therapy. Pharmacol Res 2022;22:106629.
49. Powell J, Piszczatoski C, Taylor JR. Oral semaglutide: The first-available noninjectable glucagon-like peptide 1 receptor agonist. Clin Ther 2020;42(10):2100-16.
50. Brunton SA, Mosenzon O, Wright Jr EE. Integrating oral semaglutide into clinical practice in primary care: for whom, when, and how?. Postgrad Med 2020;132(2):48-60.
51. Apperley LJ, Blackburn J, Erlandson-Parry K, et al. Childhood obesity: A review of current and future management options. Clin Endocrinol 2022;96(3):288-301.
52. Latif W, Lambrinos KJ, Rodriguez R. Compare and contrast the glucagon-like peptide-1 receptor agonists (Glp1ras). InStatPearls [Internet] 2021 Jul 5. StatPearls Publishing.
53. Weghuber D, Forslund A, Ahlström H, et al. A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity. Pediatr Obes 2020;15(7):e12624.
54. Shaban Mohamed MA, AbouKhatwa MM, Saifullah AA, et al. Risk Factors, Clinical Consequences, Prevention, and Treatment of Childhood Obesity. Children 2022;9(12):1975.
55. Yalçın N, Armut M, Çakır BK, et al. Drug-induced nutritional disorders. Clin Sci Nutr 2019;1(3):113-22.
56. Page LC, Freemark M. Role of GLP-1 receptor agonists in pediatric obesity: benefits, risks, and approaches to patient selection. Curr Obes Rep 2020;9(4):391-401.
57. Bomberg EM, Palzer EF, Rudser KD, et al. Anti-obesity medication prescriptions by race/ethnicity and use of an interpreter in a pediatric weight management clinic. Ther Adv Endocrinol Metab 2022;13:20420188221090009.
58. Berman C, Naguib M, Hegedus E, et al. Topiramate for Weight Management in Children with Severe Obesity. Child Obes 2023;19(4):219-25.
59. Pi-Sunyer X, Apovian CM, McElroy SL, et al. Psychiatric adverse events and effects on mood with prolonged-release naltrexone/bupropion combination therapy: a pooled analysis. Int J Obes 2019;43(10):2085-94.
60. Ali Ibrahim AI, Mendoza B, Stanford FC, et al. Real-World Experience of the Efficacy and Safety of Phentermine Use in Adolescents: A Case Series. Child Obes 2022;19(8):535-40.
61. Kelly AS, Bensignor MO, Hsia DS, et al. Phentermine/topiramate for the treatment of adolescent obesity. NEJM Evidence 2022;1(6):EVIDoa2200014.