Management of Monogenic and Syndromic Obesity

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KEYWORDS

• Leptin • Proopiomelanocortin • Metreleptin • Setmelanotide
• Bardet-Biedl syndrome • Prader-Willi syndrome • Ciliopathy • Syndromic obesity
• Monogenic obesity

KEY POINTS

- Monogenic defects of the leptin pathway cause severe, early childhood-onset obesity.
- Multiple syndromic obesity disorders also converge on the leptin pathway.
- Treatments targeting the leptin pathway provide a precision medicine approach to treating many of these genetic obesity disorders.

INTRODUCTION

The adipocyte-secreted hormone leptin and its downstream signaling mediators within the central nervous system (**Fig. 1**) have been fundamental in understanding energy homeostasis. Targeted pharmacotherapy (**Table 1**) has entered clinical practice for treating obesity associated with monogenetic defects of leptin, leptin receptor (LEPR), POMC, and prohormone convertase 1 and Bardet-Biedl syndrome (BBS), a group of ciliopathies that disrupts several mediators of leptin signaling. A similar precision medicine approach has led to investigational therapies for other leptin pathway defects and syndromic hyperphagic obesity disorders, including Prader-Willi syndrome (PWS).

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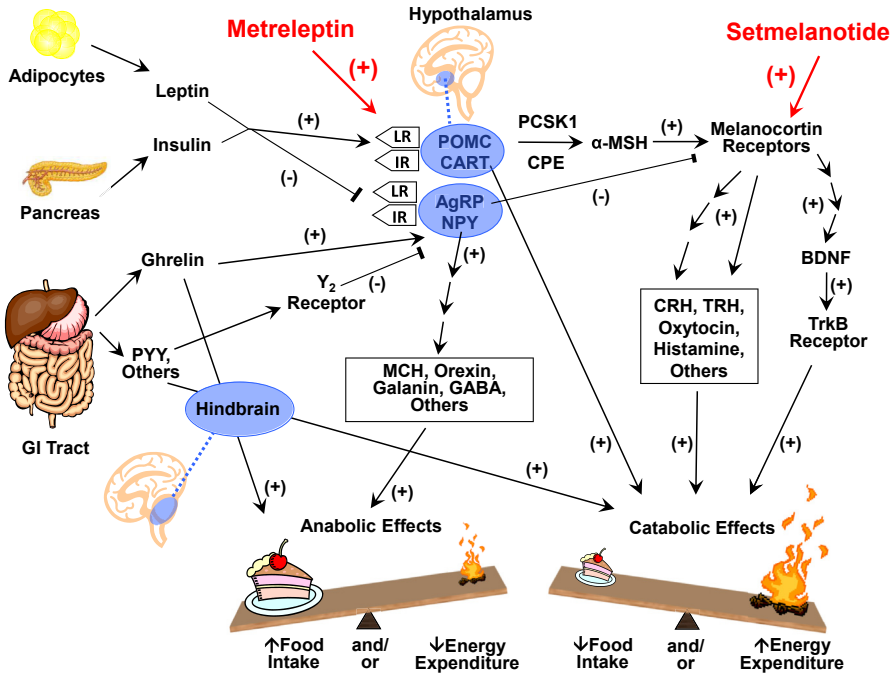

Fig. 1. Targeted sites of therapy within the leptin pathway. In this simplified diagram of the leptin pathway, *lines with arrowheads* show stimulatory action while lines with perpendicular end blocks show inhibitory action. Metreleptin is a ligand for the leptin receptor (LR). Setmelanotide is a ligand for the melanocortin-4 receptor. AgRP, agouti-related protein; BDNF, brain-derived neurotrophic factor; CART, cocaine-amphetamine related transcript; CPE, carboxypeptidase E; CRH, corticotropin-releasing hormone; GABA, gamma amino butyric acid; GI, gastrointestinal; IR, insulin receptor; LR, leptin receptor; MCH, melanin-concentrating hormone; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; PYY, peptide YY; TRH, thyrotropin-releasing hormone; TrkB, tropomyosin receptor kinase B. (Reprinted with permission from Elsevier. Han JC et al. The Lancet. 2010 May 15;375(9727):1737-48.)

METRELEPTIN FOR LEPTIN DEFICIENCY

Metreleptin is a recombinant methionyl leptin analog and has a longer half-life than endogenous leptin, permitting once-daily administration. In children with congenital leptin deficiency due to homozygous leptin gene (*LEP*) mutations – leading to undetectable, reduced, or detectable but bioinactive leptin – metreleptin induces significant weight loss due to reduced fat mass while maintaining lean body mass and statural growth.[1–4] Metreleptin also restored the neuroendocrine and immune system abnormalities associated with leptin deficiency, including central hypothyroidism, hypogonadotropic hypogonadism, and defective lymphocyte function.[2,5,6] The development of neutralizing antibodies to metreleptin has been observed, which may pose a challenge for long-term therapy.[2] Currently, the only United States Food and Drug Administration (US-FDA)-approved indication for metreleptin is the treatment of generalized lipodystrophy, which causes hypoleptinemia due to near-total absence or destruction of adipocytes. The metabolic derangements of lipodystrophy mirror those of leptin deficiency, including hyperphagia, steatohepatitis,

Table 1
Targeted pharmacotherapies for monogenic and syndromic causes of obesity converging on the leptin pathway

Monogenetic Disorders	Targeted Pharmacotherapy	Benefits	Challenges	Approved Indications (Obesity-Related)
Leptin Deficiency	Metreleptin *Recombinant methionyl leptin analogue*	Reduction of fat while maintaining lean body mass Restored immune functions associated with leptin deficiency	Development of antibodies to metreleptin may pose a challenge to long-term treatment	Only approved for lipodystrophy, not leptin deficiency or obesity
Leptin Receptor (LEPR) Deficiency Proopiomelanocortin (POMC) Deficiency Proprotein Convertase Subtilisin/Kexin Type 1 (PCSK1) Deficiency	Setmelanotide *MC4R agonist*	Unlike previous MC4R agonists, no significant cardiovascular adverse effects reported Increased resting energy expenditure, appetite suppression	Injection site reactions, skin hyperpigmentation (due to melanocortin-1 receptor activation), nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper respiratory tract infection, and spontaneous penile erection	Obesity in patients aged $\geq$6 y with LEPR, POMC, or PCSK1 deficiency
Melanocortin-4 Receptor (MC4R) Deficiency	Setmelanotide *MC4R agonist*	Specific variants of MC4R may be rescued	Targeted therapies for MC4R variants unresponsive to this analog are needed	Under investigation
Syndromic Disorders	**Targeted Pharmacotherapy**	**Benefits**	**Challenges**	**Approved Indications (Obesity-Related)**
Bardet-Biedl syndrome (BBS) Alström syndrome (AS)	Setmelanotide	Above	Above	Approved for BBS but still under investigation for AS

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Table 1
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Syndromic Disorders	Targeted Pharmacotherapy	Benefits	Challenges	Approved Indications (Obesity-Related)
PWS	Growth hormone therapy	Enhanced growth and motor development, decreased fat mass and increased lean mass, improved energy expenditure May improve neurodevelopment if begun in infancy	No significant adverse effects, but monitoring of glucose metabolism, cardiovascular disease, sleep-disordered breathing, scoliosis, and longer-term cancer risk is advised	PWS
	Liraglutide and Semaglutide *Glucagon-like peptide-1 receptor agonists*	Appetite suppression and delayed gastric emptying	Gastrointestinal disorders	Obesity in patients ≥12 y of age
	Oxytocin and Carbetocin *Neuropeptide and its synthetic analogue* PWS	May reduce appetite and social function deficits	Symptoms of anxiety, facial flushing	Under investigation
	Ghrelin modulators *Analog of unacylated ghrelin* *Inhibition of ghrelin-O-acyltransferase*	May improve hyperphagia and post-prandial glucose concentration	No significant adverse effects reported	Under investigation
	Diazoxide choline *Benzothiadiazine that acts through ATP-sensitive K+ channels*	May reduce appetite and decrease fat mass	Hypertrichosis, peripheral edema, and hyperglycemia	Under investigation
	Belanorib *Methionine aminopeptidase-2 inhibitor*	May reduce appetite and decrease fat mass	Injection site bruising, venous thrombotic events	Analogs that do not cause increased thrombosis are under investigation
	Combination of tesofensine and metoprolol *Monoamine reuptake inhibitors + beta-1 selective blocker*	May reduce appetite and body weight	Sleep disturbances, dry mouth, headache, and exacerbation of pre-existing anxiety	Under investigation with FDA Orphan Drug Designation for PWS and hypothalamic obesity

hypertriglyceridemia, severe insulin resistance, and type 2 diabetes which are all ameliorated by metreleptin therapy.[7,8]

SETMELANOTIDE FOR LEPR, POMC, AND PCSK1 DEFICIENCIES

Binding of leptin to the LEPR leads activation of neurons that express POMC, a peptide prohormone that is cleaved by PCSK1 to produce α-melanocyte-stimulating hormone (α-MSH), the endogenous ligand of the melanocortin-4 receptor (MC4R), and several other peptides, and adrenocorticotrophic hormone (ACTH). Biallelic deleterious mutations of the genes encoding LEPR, POMC, and PCSK1 cause rare autosomal recessive monogenic obesity, characterized by severe hyperphagia and development of obesity in early childhood. Clinically, LEPR deficiency is similar in phenotype to leptin deficiency.[9,10] POMC deficiency is associated with adrenal insufficiency due to ACTH deficiency and hypopigmentation because of melanin induced by α-MSH activation of the melanocortin-1 receptor (MC1R) in skin and hair.[11] PCSK1 deficiency causes reduced processing of several other prohormone peptides besides POMC, including proglucagon and proinsulin, conferring additional features, including malabsorptive diarrhea and post-prandial hyperglycemia due to insulin insufficiency, followed by hypoglycemia mediated by elevated residual proinsulin.[12,13]

Unlike earlier MC4R agonists which induced hypertension and tachycardia as untoward side effects,[14] setmelanotide is an MC1R and MC4R agonist that avoids appreciable sympathetic nervous system activation in primates, making it an attractive therapeutic for bypassing the deficits caused by LEPR, POMC, and PCSK1 deficiencies.[15,16] In adults with obesity and no known genetic abnormalities, short-term 72-h setmelanotide administration increased resting-energy expenditure without adverse cardiovascular effects.[17] In a 4-week randomized-controlled trial (RCT), setmelanotide induced a modest 4% (placebo-subtracted) reduction in weight.[16] Studies of setmelanotide soon followed in patients with genetic conditions affecting the leptin-melanocortin pathway. In open-label trials of patients aged ≥6 years with LEPR, POMC, or PCSK1 deficiency, setmelanotide significantly reduced hunger and induced at least 10% weight loss at ~12 months in 45% of patients with LEPR deficiency, 80% of patients with POMC deficiency, and 80% of patients with PCSK1 deficiency.[18,19] Common adverse events included injection-site reactions, skin hyperpigmentation (due to MC1R activation), nausea, headache, diarrhea, abdominal pain, back pain, fatigue, vomiting, depression, upper-respiratory-tract infection, and spontaneous penile erection.[20] Setmelanotide received US-FDA approval in November 2020 for treatment of obesity in patients aged ≥6 years with LEPR, POMC, or PCSK1 deficiency. The efficacy of setmelanotide for treatment of obesity associated with deficiency of carboxypeptidase E, an additional processing enzyme for PCSK1, is currently under investigation (ClinicalTrials.gov Identifier: NCT04963231).[21]

MC4R DEFICIENCY

Mutations of MC4R that impair its synthesis, plasma membrane expression, ligand binding capacity, intracellular signaling, or recycling after endocytosis can cause obesity in an autosomal dominant pattern of inheritance.[22] Homozygous and compound heterozygous (ie, biallelic) *MC4R* mutations are rare and cause extreme obesity, while heterozygous mutations cause less severe obesity and are fairly common, reported in approximately 3% of patients with childhood-onset obesity.[23,24] Interventions used in common forms of obesity, such as liraglutide, phentermine, and bariatric surgery, may have some short-term efficacy in individuals with MC4R mutations, but a frequent observation is attenuated responsiveness and weight regain,

particularly for patients with biallelic MC4R mutations.[25–29] Targeted therapies are therefore needed. Setmelanotide did not induce statistically significant weight loss in a small cohort of adults with a variety of heterozygous MC4R mutations, but whether genotype-specific responsiveness in vitro for the greater-than-350 MC4R known variants can predict responsiveness in vivo remains to be explored.[16] Novel investigations include translational readthrough enhancers to overcome stop codons, chaperones to enhance misfolded receptor trafficking, modifiers of dimerization, and targeting of downstream signaling mediators.[30,31]

CILIOPATHIES CONVERGING ON THE LEPTIN PATHWAY

BBS and Alström syndrome (AS) are rare, autosomal recessive ciliopathies caused by mutations in one of greater-than-20 BBS genes (*BBS1-BBS22*) or the *ALMS1* gene. Patients develop early childhood-onset hyperphagia[32] and obesity plus retinal dystrophy, renal disease, and gonadal dysfunction.[33,34] Patients with BBS also typically have polydactyly and intellectual deficiency,[33] while AS is often associated with hearing loss and cardiomyopathy but preserved cognitive function.[34,35] The mechanism for the appetite dysregulation and weight gain in both BBS and AS is attributed to leptin resistance[36,37] due to the role of cilia in LEPR transport to the plasma membrane and POMC neuronal survival and function.[38–40] Bypassing the defects in LEPR and POMC of patients with ciliopathy disorders by activation of MC4R with setmelanotide has been demonstrated to be an effective approach. In an open-label study of patients with BBS aged $\geq$12 years, setmelanotide treatment for 52 weeks resulted in 16.3% weight loss after 52 weeks.[41] In a subsequent RCT, 32.3% of patients with BBS had at least a 10% reduction in body weight after 52 weeks of setmelanotide with a mean reduction in weight by 9.5%.[42] Setmelanotide received FDA approval for the treatment of obesity in patients with BBS in June 2022.

Investigations of setmelanotide in AS have been hampered by low enrollment due the rarity of the condition,[43] but preliminary data of combined 8 patients with AS enrolled in phase 2 and 3 studies (ClinicalTrials.gov Identifiers: NCT03013543, NCT03746522) showed that in patients who received setmelanotide for 9.7 to 18.2 months, 1 of 2 adults (50%) had $\geq$25% decrease in hunger score; 5 of 6 (83.3%) youth younger than 18 years achieved $\geq$0.2 decrease in body mass index (BMI) Z-score; 3 of 4 patients (75%) aged $\geq$12 to less than 18 years achieved $\geq$25% hunger score decrease; 2 of 8 patients (25%) had improved QOL. Overall, 7 of 8 patients (87.5%) had improvement in at least one of the outcome domains. These findings are encouraging and warrant further studies of setmelanotide in AS, in particular, the role of patient genotype or other characteristics as predictors of response.[44]

Specific dietary recommendations may also benefit BBS and AS because both are associated with insulin resistance that is more severe than expected for degree of adiposity,[36,37] which may be attributable to the role of primary cilia in insulin receptor signaling.[45] Therefore, caloric portion control, physical activity, and limiting of simple carbohydrate intake are recommended in patients with ciliopathy-associated obesity.[35,46] Data regarding the safety and efficacy of bariatric surgery in such patients are limited, with a few case reports showing moderate weight loss but of uncertain sustainability[29] and lack of impact on type 2 diabetes control in the case of gastric banding.[47,48]

TREATMENT OF PRADER-WILLI SYNDROME

PWS is caused by a lack of expression of paternal genes located in the chromosome 15q11.2-q13 region caused by paternal gene deletion (70%), maternal uniparental disomy (25%), or imprinting defects (5%).[49] PWS is characterized by poor feeding during

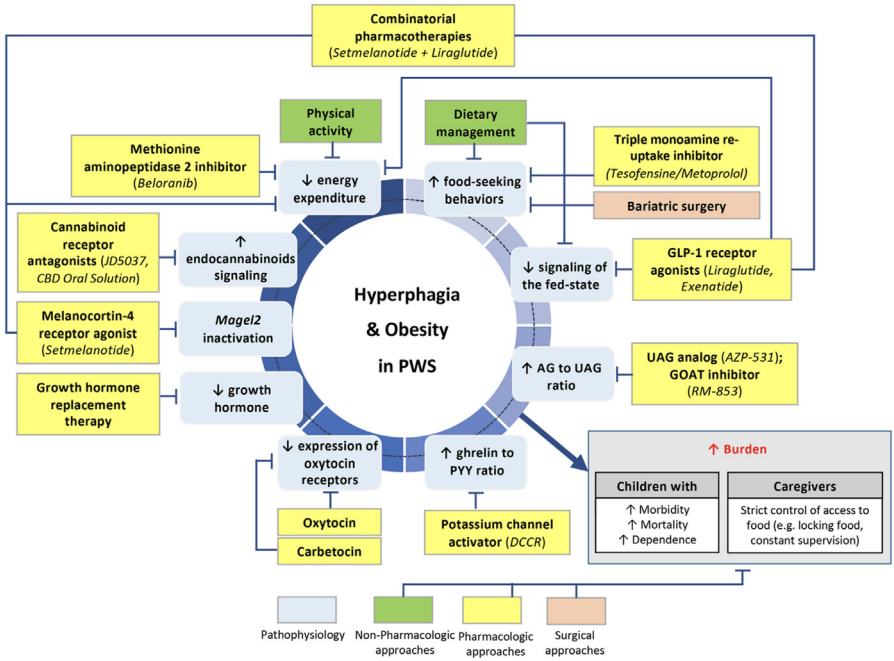

Fig. 2. Pathophysiology of Prader-Willi syndrome and treatment approaches. Emerging therapies under investigation for the treatment of hyperphagia and obesity in Prader-Willi syndrome include pharmacologic (medication names shown in italics), nonpharmacologic, and surgical approaches to target specific mechanistic aspects of the syndrome. AG, acylated ghrelin; AG, unacylated ghrelin; DCCR, diazoxide choline controlled release; GLP-1, glucagon-like peptide 1; GOAT, ghrelin O-acyltransferase; PYY, peptide YY. (*From* Tan, Q, Orsso, CE, Deehan, EC, et al. Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: A narrative review. Obesity Reviews. 2020; 21:e12992. https://doi.org/10.1111/obr.12992.)

infancy, followed by progressive weight gain, lack of satiety, and constant food-seeking behaviors. A framework for PWS management is shown in **Fig. 2**.

Nutrition Recommendations in Prader-Willi Syndrome

Involvement of parents and all caregivers is necessary to have control of the environment with regard to food access and consistent scheduling of meals and snacks consumption and physical activity.[50] Restriction of food access is necessary to prevent hyperphagic overeating, which can become so severe if unmonitored as to cause gastric necrosis.[51] Establishing a routine for timing of food intake is beneficial for reducing anxiety about food access and preventing behavior problems, such as temper tantrums, manipulation, and sneaking.[52]

Energy needs are less in individuals with PWS due to lower lean muscle mass and higher percentage body fat than age-, sex-, and BMI-matched controls.[53,54] Therefore, dietary recommendations for infants and children with PWS are approximately 20% to 40% fewer calories to maintain energy balance than for healthy individuals of the same age.[53,55] For weight maintenance, 10.0 to 14.0 kcal/cm of height is recommended, and for weight reduction, 7 to 9 kcal/cm of height.[56,57] Close monitoring is necessary to prevent overrestriction, which could worsen hunger drive and

behavioral exacerbations and cause micronutrient deficiencies.[58] Lower carbohydrate consumption and higher dietary fiber intake (at least 20 g/day) have been generally recommended for patients with PWS,[59] but even stricter limitation of carbohydrates in favor of increased proportion of calories from fats (15% carbohydrates; 65% fat; 20% protein) while still adhering to overall energy-reduced intake has been proposed as a beneficial approach for reducing the ratio of ghrelin (an orexigenic peptide that is higher in PWS) to glucagon-like peptide 1 (GLP-1, an anorexigenic peptide that also improves beta-cell function and insulin sensitivity), thereby reducing hunger drive and improving glycemic control.[60] Increasing fiber intake even further to 40 g/day has been proposed based on the premise that fermentation of dietary fiber by gut bacteria produces short-chain fatty acids, which promote expression and secretion of GLP-1 and another anorexigenic intestinal hormone, peptide YY.[61] Thus, modulation of the gut by dietary fiber could be a potential treatment strategy in PWS and is currently under investigation (ClinicalTrials.gov Identifier: NCT04150991).

Individuals with PWS have a tendency to prefer sweetened beverages over plain water,[62] but recommending the use of nonnutritive sweeteners should be approached with caution and avoided if possible due to the potential negative impact on the intestinal microbiome and the hedonic response to sweetness, which could worsen hunger.[63,64] Probiotic supplementation has been proposed, but studies are limited to short-term trials. A 4-week randomized controlled crossover study examining probiotics for treatment of constipation in PWS showed minimal effect on laxation and microbiota composition.[65] A 12-week RCT in 71 individuals with PWS resulted in BMI reduction and improvements in neurodevelopmental measures within the probiotic group.[66] Further studies are needed to assess optimal diet composition for weight management in PWS.

Growth hormone therapy in Prader-Willi syndrome

Short stature and growth hormone (GH) deficiency are common patients with PWS.[67] GH therapy, approved for growth promotion in children with PWS by the US-FDA and Health Canada, has positive benefits during childhood on height, motor development, body composition (decreased fat mass and increased lean mass), and energy expenditure,[68] plus potential benefits for neurodevelopment when begun in infancy in some studies.[69] In adults with PWS, GH treatment has continued benefits on body composition, muscle strength, exercise capacity, and quality of life.[70,71] Current standards of care in PWS support the early use of GH therapy as soon as possible after genetic confirmation of PWS diagnosis.[72,73] Treatment has generally been safe with no significant adverse effects on glucose metabolism, cardiovascular disease, sleep-disordered breathing, scoliosis, or longer-term cancer risk, although close monitoring for these complications is still advised.[74]

Glucagon-like peptide-1 receptor agonists in Prader-Willi syndrome

GLP-1 receptor agonists (GLP1RAs) induce weight loss via appetite suppression and delayed gastric emptying. A systematic review of 10 studies summarizing nonrandomized exenatide or liraglutide use in 23 patients with PWS (aged 13–37 years) over 14 weeks to 4 years reported improvements in BMI (1.5–16 kg/m^2), hemoglobin A1C in 19 of 23 cases, and satiety.[75] A recently published RCT including 55 children and adolescents with PWS who received 3 mg (or maximum tolerated dose) liraglutide or placebo (randomized 2:1) for 16 weeks followed by liraglutide for 52 weeks while participating in a structured diet and exercise program.[76] There were no significant differences between groups for change in BMI SDS (for age and sex standards) at 16 or

52 weeks, although hyperphagia was lower in adolescents treated with liraglutide than placebo at 52 weeks.[76] The most common adverse events with liraglutide were gastrointestinal disorders.[76] RCTs of more potent GLP1RAs, such as semaglutide, or combination therapies such as glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor dual agonists (eg, tirzepatide) or GLP-1/GIP/glucagon receptor triagonists (eg, SAR441255)[77] have yet to be explored in PWS. In a case series of 2 patients with PWS who received semaglutide, BMI SDS increased in one and decreased in the other.[78]

Melanocortin-4 receptor agonist in Prader-Willi syndrome

Magel2 is a gene within the PWS chromosome 15 critical region.[49] Magel2-deficient mice have a POMC deficit responsive to pharmacologic treatment with the MC4R agonist setmelanotide.[79] Setmelanotide is currently being investigated as a treatment for hyperphagia and obesity in patients with PWS (ClinicalTrials.gov Identifier: NCT02311673).

Oxytocin and carbetocin in Prader-Willi syndrome

Oxytocin is a neuropeptide that plays a key role in human social behaviors, including parental bonding, trust, and regulation of feeding.[80] Reduced hypothalamic oxytocin-expressing neurons has been observed in PWS,[81] suggesting a potential role in the hyperphagia, anxiety, and social deficits of PWS.[82] Intranasal administration of oxytocin in patients with PWS has been reported as well tolerated and safe, but effects on hyperphagia and social function have been mixed, with possible differences in response based on sex and PWS subtype.[83–88]

Carbetocin is a synthetic analog of oxytocin that is more selective for the oxytocin receptor, which may confer benefits over oxytocin as oxytocin's partial agonism at the arginine vasopressin receptor could contribute to anxiogenic side effects of oxytocin.[85] The results of the largest RCT to date of intranasal carbetocin in 119 patients with PWS (aged 7–18 years) reported that the 8-week placebo-controlled period of the study (carbetocin 9.6 mg, carbetocin 3.2 mg, or matching placebo by nasal spray TID with meals) showed no difference in weight changes between groups; the carbetocin 3.2-mg group (though not the higher 9.6 mg arm) demonstrated significant improvements in hyperphagia, Clinical Global Impression, and PWS Anxiety and Distress Questionnaire, with benefits sustained in the 56-week follow-up period of open-label carbetocin treatment.[89] Intranasal carbetocin was well-tolerated, with flushing as the most frequent adverse event reported.[89]

Ghrelin modulation in Prader-Willi syndrome

Elevation of the active acylated form of the orexigen ghrelin has been observed in PWS,[90] leading to the hypothesis that competitive inhibition using an analog of unacylated ghrelin could oppose the appetite-increasing effect of endogenous acylated ghrelin. Livoletide (AZP-531), a cyclic 8 amino acid analog of unacylated ghrelin A, was observed in a 14-day RCT of 47 patients with PWS (aged 12–50 years) to improve hyperphagia and post-prandial glucose concentration compared to placebo.[91] Livoletide was well-tolerated with no serious side effects. A lack of effect on hyperphagia and body weight of livoletide in a subsequent 12-week RCT led to discontinuation of further studies for this medication.[92]

Inhibition of ghrelin-O-acyltransferase, the enzyme which catalyzes ghrelin acylation, has been studied using GLWL-01 administered at 450 mg po BID in a 28-day double-blind, placebo-controlled phase 2 crossover study in 19 patients with PWS.[93] GLWL-01 treatment resulted in a significant reduction in acylated ghrelin, but hyperphagia, eating behaviors, BMI, and metabolic parameters were unchanged. Further longer-term studies are required.

Diazoxide in Prader-Willi syndrome

Diazoxide choline is a benzothiadiazine that acts through ATP-sensitive K+ channels (KATP) and is used for treatment of hyperinsulinemic hypoglycemia. It may exert therapeutic effects in PWS through downregulation of insulin from pancreatic β-cells, decrease in hypothalamic neuropeptide Y concentrations, increase in GABAergic neurons, and/or activation of KATP channels in adipocytes.[94] Diazoxide choline-controlled release (DCCR) is an extended-release form of diazoxide choline. In a 13-week randomized, double-blind, placebo-controlled phase 3 trial, DCCR significantly reduced fat mass ($P = .003$) but without significant difference in BMI.[95] Hyperphagia improved only in patients with severe hyperphagia at baseline.[95] The most common DCCR-associated side effects were hypertrichosis, peripheral edema, and hyperglycemia.[95] Long-term studies are needed.

Methionine aminopeptidase-2 inhibitor (belanorib) in Prader-Willi syndrome

Belanorib is an irreversible inhibitor of methionine aminopeptidase-2 (MetAP2), an enzyme that is implicated in cell growth and angiogenesis. Inhibition of MetAP2 leads to weight loss through several proposed mechanisms, including decreased caloric intake,[96] increased fat mobilization and oxidation, suppression of endothelial cell proliferation,[97] and prevention of adipose tissue expansion.[98] A 26-week phase 3 randomized, double-blind, placebo-controlled trial was conducted of belanorib in 107 participants with PWS (aged 12–65 years).[99] Patients were randomly assigned (1:1:1) to biweekly placebo (n = 34), 1.8 mg of belanorib (n = 36), or 2.4 mg of belanorib (n = 37). Improvement in hyperphagia was seen in the 1.8- and 2.4-mg belanorib groups ($P = .0003$ and $P = .0001$ vs placebo). In addition, weight loss was greater with 1.8 mg or 2.4 mg of belanorib ($P < .0001$ vs placebo). Injection-site bruising was the most common adverse event. However, the trial was terminated early due to venous thrombotic events in the belanorib-treated participants (two with fatal pulmonary embolism). Next-generation MetAP2 inhibitors are under investigation with efficacy for weight loss but with better safety profiles as the goal.

Combination tesofensine and metoprolol in Prader-Willi syndrome

The FDA granted orphan drug designation for fixed-dose combination of tesofensine and metoprolol in PWS in March 2021 and hypothalamic obesity in July 2021. Tesofensine is a centrally acting monoamine reuptake inhibitor that blocks the presynaptic reuptake of dopamine, serotonin, and noradrenaline. Metoprolol is a beta-1 selective blocker dosed at a ratio of 100:1 in combination with tesofensine to prevent adverse cardiovascular effects (tachycardia and hypertension) commonly associated with tesofensine and other monoamine reuptake inhibitors, such as sibutramine. In unpublished data (https://www.globenewswire.com/news-release/2021/03/03/2186073/0/en/Saniona-Receives-U-S-FDA-Orphan-Drug-Designation-for-Tesomet-in-Prader-Willi-Syndrome.html) supplied by the manufacturer from a randomized, double-blind, placebo-controlled phase 2a trial (ClinicalTrials.gov Identifier: NCT03149445), adults with PWS receiving tesofensine/metoprolol had a statistically significant reduction in hyperphagia and a clinically meaningful reduction in body weight at a dose of 0.5 mg of tesofensine/50 mg of metoprolol daily while adolescents with PWS had positive responses at lower doses.[100] The only published data on tesofensine/metoprolol are from a study of 21 adults with hypothalamic obesity randomized to receive 0.5 mg of tesofensine/50 mg of metoprolol or placebo for 24 weeks.[101] Adverse events associated with tesofensine/metoprolol included sleep disturbances, dry mouth, headache, and exacerbation of pre-existing anxiety. There were no significant differences in heart rate or blood pressure between treatment groups. The difference

between tesofensine/metoprolol and placebo was a mean weight change of −6.3% (95% CI: −11.3, −1.3; P = .017). A phase 2b clinical trial in patients with PWS (ClinicalTrials.gov Identifier: NCT05198362) was initiated in December 2021 but voluntarily suspended by the manufacturer in March 2022 due to financial constraints.

OTHER ANTI-OBESITY MEDICATIONS IN PRADER-WILLI SYNDROME

Currently available FDA-approved long-term medications for obesity treatment in the general population include orlistat, GLP1RAs (liraglutide, semaglutide), and phentermine/topiramate for patients aged ≥12 years and bupropion/naltrexone in adults. Data for orlistat in PWS are lacking in the extant literature. GLP1RAs in PWS are discussed previously. Data for phentermine/topiramate and bupropion/naltrexone in PWS are limited to case series reports,[101,102] but overall, these medications appear to show efficacy and safety profiles in PWS similar to the general population although discontinuation rates were high, particularly for phentermine/topiramate due to side effects, and weight regain occurred with discontinuation. The endocannabinoid receptor CB1 antagonist, rimonabant, which had been initially approved for the treatment of obesity in Europe in 2006, was postulated to be particularly beneficial in individuals with PWS too because of the increased endocannabinoid tone that has been observed in PWS.[103] However, the severe adverse psychiatric effects observed in the general population, as well as in patients with PWS,[104] led to withdrawal of rimonabant from clinical use in 2008. Peripherally restricted endocannabinoid receptor CB1 antagonists have been proposed as a potential alternative approach that may avoid these side effects, but no data from clinical trials have been reported to date.[103]

Bariatric Surgery in Prader-Willi Syndrome

A recent systematic review of metabolic and bariatric surgery (MBS) in PWS (67 patients from 22 articles evaluated outcomes of laparoscopic sleeve gastrectomy (LSG), gastric bypass (GB), and biliopancreatic diversion (BPD). No mortality within 1 year was reported in any of the 3 groups after a primary MBS operation. All groups experienced a significant decrease in BMI at 1 year with a mean reduction in BMI of 14.7 kg/m^2 (P < .001) with sustained weight loss in the LSG, GB, and BPD groups for up to 3, 2, and 7 years, respectively.[105] Iron deficiency was reported for 1 patient in the LSG group and 1 patient in the BPD group; 2 cases of osteoporosis were reported in the BPD group.[105] No nutritional deficiencies were reported in the GB group.[105] Additional long-term studies are needed for the safety and efficacy of bariatric surgery in PWS.

CONCLUSIONS AND FUTURE DIRECTIONS

Bypassing defects within the leptin signaling pathway is an effective approach for obesity treatment in specific disorders: metreleptin for leptin deficiency and setmelanotide for defects of the LEPR, POMC, and its processor, PCSK1, as well as ciliopathies that affect the leptin pathway. Whether this approach may be beneficial for treating obesity in heterozygous carriers of common variants in these same genes is under investigation (ClinicalTrials.gov Identifier: NCT05093634). Furthermore, emerging combination of anti-obesity drugs such as tirzepatide (GIP/GLP1RAs) or retatrutide (GIP/GLP-1/glucagon receptor triagonist) warrant further study in genetic obesity conditions. Finally, novel approaches of targeting downstream mediators of the leptin pathway, such as brain-derived neurotrophic factor (BDNF), show promise. In a Magel2-null mouse model for PWS, adeno-associate virusmediated hypothalamic

gene transfer of BDNF decreased fat mass without inducing cachexia due to an autoregulatory mechanism in which silencing RNA for BDNF is produced under the control of an agouti-related protein (AgRP) responsive promoter that is activated by the increase in AgRP secretion that occurs in the setting of excessive weight loss.[106] Augmenting BDNF and other downstream mediators of the leptin pathway hold potential for the treatment of other genetic causes of obesity beyond PWS as there are dozens of other syndromic conditions associated with obesity for which such an approach could be beneficial.[107]

CLINICS CARE POINTS

- Metreleptin, a leptin analogue with a longer half-life, reduces adiposity in patients with leptin deficiency, but the development of neutralizing antibodies may diminish efficacy.
- Setmelanotide, a melanocortin-4 receptor agonist, is FDA-approved for the treatment of obesity in patients aged ≥6 years with LEPR, POMC, or PCSK1 deficiency or who have Bardet-Biedl syndrome.
- In patients with Prader-Willi syndrome, growth hormone increases lean mass and reduces adiposity. Liraglutide and semaglutide, glucagon-like peptide-1 receptor agonists, reduce appetite, but their effect on BMI in PWS is equivocal. Multiple studies of investigational therapies for PWS are currently ongoing.

DISCLOSURE

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