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Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: A narrative review

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Summary

In early childhood, individuals with Prader-Willi syndrome (PWS) experience excess weight gain and severe hyperphagia with food compulsivity, which often leads to early onset morbid obesity. Effective treatments for appetite suppression and weight control are currently unavailable for PWS. Our aim to further understand the pathogenesis of PWS led us to carry out a comprehensive search of the current and emerging therapies for managing hyperphagia and extreme weight gain in PWS. A literature search was performed using PubMed and the following keywords: "PWS" AND "therapy" OR "[drug name]"; reference lists, pharmaceutical websites, and the ClinicalTrials.gov registry were also reviewed. Articles presenting data from current standard treatments in PWS and also clinical trials of pharmacological agents in the pipeline were selected. Current standard treatments include dietary restriction/-modifications, exercise, and growth hormone replacement, which appear to have limited efficacy for appetite and weight control in patients with PWS. The long-term safety and effectiveness of bariatric surgery in PWS remains unknown. However, many promising pharmacotherapies are in development and, if approved, will bring much needed choices into the PWS pharmacological armamentarium. With the progress that is currently being made in our understanding of PWS, an effective treatment may not be far off.

KEYWORDS
hyperphagia, obesity, Prader-Willi syndrome, therapy

1 | INTRODUCTION

Prader-Willi Syndrome (PWS) is a complex neurodevelopmental genetic disorder resulting from absence of expression of imprinted genes in the paternally derived region of the chromosome 15q11.2-q13.[1] PWS is the most common syndromic cause of life-threatening obesity with an estimated incidence of 1/10 000 to 1/25 000 live births, occurring equally in both males and females, and across all ethnicities.[1] The errors in genomic imprinting that are causative for PWS (determined by a DNA methylation analysis) are

ABBREVIATIONS: ACTH, corticotrophin; AG, acylated ghrelin; AVP, arginine vasopressin; BMI, body mass index; CB1R, cannabinoid type 1 receptors; CBD, cannabidiol; DCCR, diazoxide choline controlled release; eCB, endocannabinoid; FDA, Federal Drug Agency; GH, growth hormone; GHSR-1a, growth hormone secretagogue receptor type 1a; GLP-1, glucagon-like peptide-1; GOAT, ghrelin *O*-acyltransferase; HbA1c, haemoglobin A1c; HO, hypothalamic obesity; ID, imprinting centre defect; LMGBP, laparoscopic minigastric bypass; LSG, laparoscopic sleeve gastrectomy; MC4R, melanocortin-4 receptor; MetAP2, methionine aminopeptidase 2; MSHs, melanocyte-stimulating hormones; OSA, obstructive sleep apnoea; OXY, oxytocin; POMC, pro-opiomelanocortin; PP, pancreatic polypeptide; PWS, Prader-Willi syndrome; PYY, peptide YY; RQ, respiratory quotient; T2DM, type 2 diabetes mellitus; UAG, unacylated ghrelin; UPD, uniparental disomy.

classified as *paternal deletion*, which represents the majority of all cases of PWS (60%); *maternal uniparental disomy* (*UPD*) *15*, found in about 36%; and *imprinting centre defect* (*ID*), in 4%.[2]

Major characteristics of PWS include infantile lethargy and hypotonia causing poor feeding and failure to thrive, followed by excess weight gain and onset of hyperphagia in early childhood, in addition to hypogonadism, global development delay, minor facial abnormalities (ie, a narrow forehead, almond-shaped eyes, and a triangular mouth), and mild to moderate mental retardation. Additional features may present, such as sleep disorders, behavioural and psychiatric disturbances, short stature, small hands and feet, hypopigmentation, and skin picking. Strabismus and scoliosis may also manifest and become more pronounced with age.[3]

PWS was first described by two Swiss paediatric endocrinologists, Andrea Prader and Heinrich Willi, along with an internist, Alexis Labhart, in 1956.[4] This collaboration resulted in the first evidence-based publication about the syndrome; this later enhanced efforts to help advance the understanding of the causes of mortality in individuals with PWS and develop therapies to improve overall quality of life. The purpose of this review is to provide an evidence-based update of therapy options for the management of hyperphagia and obesity in PWS.

1.1 | Hyperphagia and obesity in PWS

During early infancy, individuals with PWS have hypotonia with difficulty feeding and severely decreased appetite; assisted feeding is often required for the first few months of life due to failure to thrive.[5] From 9 to 25 months of age, their appetite improves, and these infants grow steadily along the growth curve with normal feeding. Beginning in early childhood, they experience rapid weight gain with no change in appetite (appetite still appropriate for age). However, in the following phase, excessive weight gain continues and appetite increases; obesity usually develops if eating is not externally controlled. From 8 years of age onward, individuals with PWS typically begin to have the extreme unsatisfied drive to consume food, called hyperphagia, which is accompanied by lack of satiety, food preoccupations, and food-related behaviour problems. Food hoarding or foraging, eating of inedibles, and stealing of food or money to buy food are common. Individuals with PWS require absolute control through one-to-one supervision to prevent choking and binge eating, which can lead to stomach rupture, gastric necrosis, and death.[6] Excess energy intake can result in early onset morbid obesity and obesity-associated complications, which are common causes of death in PWS.[7] A few patients have a noticeable improvement in their appetite control and are able to feel full after they enter adulthood. For most patients with PWS, hyperphagia continues into adulthood, posing persistent, life-long risks to their health and safety. A frustrated lifetime of control and restricted lifestyle hinders their independence and significantly lowers the quality of life of these patients and their families.[5,7]

Although many efforts have been made to understand it, the pathophysiology of hyperphagia and obesity in PWS remains unclear. It may be explained partly by hypothalamic endocrine dysfunction. Individuals with PWS have uniquely increased concentrations of the stomach-derived orexigenic peptide hormone ghrelin and the ratio of ghrelin to peptide YY (PYY).[8-10] Serum leptin levels, which are significantly, positively correlated with body weight, are found to be high in patients with PWS.[11] In addition, these patients have lower fasting and postprandial insulin levels than that of healthy controls with obesity. The presence of other hypothalamic dysfunction-induced endocrinopathies, in particular growth hormone (GH) deficiency, also aggravates weight gain.[11] Recent studies of atypical microdeletions in PWS have suggested that the absence of the SNORD116 cluster on paternal chromosome 15q11.2 is highly contributive to the presentation of the PWS phenotype.[12,13] A mouse model of PWS found that adult mice developed hyperphagia and obesity following the *Snord116* deletion in their mediobasal hypothalamus, indicating that *Snord116* plays a role in the hypothalamic control of appetite and food intake.[14] However, the specific targets of this gene cluster in the human brain, which affect appetite, and neuroendocrine and other brain functions, have not yet been identified.

Hyperphagia in PWS is assessed using the validated *Dykens Hyperphagia Questionnaire*, which is considered the gold standard tool for measuring outcomes in PWS clinical trials.[15] Common behaviours identified by this questionnaire in PWS include extreme levels of food seeking, preoccupation with food, decreased satiety, psychic distress, eating in the absence of hunger, and binge eating.

2 | METHOD

An English-language search of the PubMed database was conducted in September 2019, with no date limits, using the terms "PWS" AND "therapy" OR "[drug name]." Results were screened for articles presenting data from current standard treatments in PWS and clinical trials of pharmacological agents in the pipeline. Reference lists and pharmaceutical companies' websites were reviewed to detect relevant sources, including unpublished study results, ongoing clinical trials, and research plans. Additionally, the ClinicalTrials.gov registry was used to identify ongoing clinical trials. Articles were also added based on the authors' knowledge of the area.

3 | RESULTS

3.1 | Current therapeutic approaches

3.1.1 | Dietary management

Individuals with PWS characteristically display an increased interest in food in early childhood and develop hyperphagia, typically accompanied by food seeking and lack of satiety.[5] Hyperphagia in patients with PWS typically results in uncontrollable weight gain and morbid obesity, which in turn leads to the development of metabolic syndrome, type 2 diabetes mellitus (T2DM), sleep apnoea, respiratory insufficiency, and cardiovascular disease during adulthood.[16] Consequently, restriction of dietary intake is fundamental for the prevention of obesity, health complications, and early death. The life-threatening drive for food in PWS is a source of stress not only for individuals with PWS but also for their caregivers. When compared with caregivers of individuals with disabilities, those who care for adolescents and young adults with PWS have reported the highest level of caregiver burden due to the need to strictly control patients' food intake.[17,18] Patients may engage in relentless food-seeking behaviours, such as stealing, foraging, and food hoarding; hence, interventions often emphasize restricting food access with behavioural modifications.[7]

Multiple diets have been developed for individuals with PWS.[19-21] A common feature of these diets is to limit energy intake to less than that recommended for healthy children and youth of the same age. When compared with age-, sex-, and body mass index (BMI)-matched controls, individuals with PWS are known to have reduced resting energy expenditure and activity energy expenditure which is partially attributable to hormone dysfunction and altered body composition characterized by lower muscle mass and excessive fat mass.[22,23] Thus, infants and children with PWS need approximately 20% to 40% less calories than those without PWS to maintain energy balance.[24] Additionally, an observational study noted that patients with PWS had a higher respiratory quotient (RQ) relative to healthy developing toddlers, indicating that patients with PWS preferentially metabolize dietary carbohydrate over dietary lipids to sustain energy homeostasis.[5] Due to lower fat oxidation, extra dietary carbohydrates can potentially lead to excess fat deposition in patients with PWS. Individuals with PWS were also found to have a preference for simple carbohydrates.[25-27] Although limited, evidence suggests excessive carbohydrate intake, particularly simple carbohydrates, may contribute to weight gain before the onset of hyperphagia in children with PWS.[21,27]

When dietary intake of youth with PWS were compared with those without PWS using 3-day food records, nutrient intakes were found to be similar in the two groups despite lower energy intake in patients with PWS.[28] This was due to the youth with PWS having better diet quality as a result of higher adherence to healthy eating guidelines. However, fibre and micronutrient intakes of more than half of youth with PWS were below recommendations, emphasizing the importance of nutrient-dense foods and dietary supplements in this population. Moreover, a few studies have investigated the role of diet macronutrient composition in weight management and the potential of its modification as an approach to fight obesity in PWS. Miller et al evaluated the effect of an energy-restricted diet with modified macronutrient distribution on body composition and weight in young children with PWS.[21] Of the 63 children (aged 2-10 years) who participated in their study, 33 children adhered to the implemented diet, which was composed of 30% fat, 45% carbohydrates, and 25% protein, with at least 20 g of fibre per day. The study showed that, for the remaining children who were compliant only with reducing energy intake, their dietary macronutrient composition was 10% to 23% fat, 50% to 70% carbohydrates, and 15% to 20% protein, with 12 g or less of fibre per day. Children consuming the recommended diet had significant improvements in body fat ($P < .0001$) and weight management ($P < .001$) with a lower RQ ($P = .002$) than those on a diet with only the reduction of energy intake. Overall, this study demonstrated that children with PWS may benefit from an energy-restricted, well-balanced diet with lower-carbohydrate consumption and higher dietary fibre intake.

Very recently, Irizarry et al examined the impact of carbohydrate restriction on hyperphagia and adiposity in children with PWS.[27] Children with PWS (n = 8, age 9-18 years) were randomly assigned to either the low carbohydrate, high-fat (LC, 15% carb; 65% fat; 20% protein) diet or the low-fat, high carbohydrate (LF, 65% carb, 15% fat, 20% protein) diet during a first hospital admission and the second diet during a subsequent admission. In comparison with those consuming the LF diet, patients on the LC diet had increased glucagon-like peptide-1 (GLP-1) ($P < .05$), reduced ghrelin ($P < .05$), and a reduced ratio of fasting ghrelin to GLP-1 ($P = .0008$), which might contribute to lower food intake and improve glycaemic control. Interestingly, the study also detected higher concentrations of free fatty acids ($P < .01$) and even-chain acylcarnitines ($P < .001$) but a lower triglycerides/high-density lipoprotein cholesterol ratio ($P < .01$) in the LC group, suggesting enhanced fat mobilization and oxidation and improved insulin resistance (reduction in postprandial insulin concentrations). These results warrant future clinical trial studies to confirm the effects of low carbohydrate diet on the regulation of food intake and weight gain in individuals with PWS.

Emerging evidence has shown that diets rich in nondigestible carbohydrates, such as dietary fibres, may be beneficial for patients with PWS. Zhang et al conducted a hospitalized intervention trial in children (aged 3-16 years) with PWS (n = 17) and those with non-syndromic obesity (n = 21).[29] They found that children with genetic and idiopathic obesity shared similar dysbiotic gut bacterial communities, in which genomes that encode genes for toxin production and pathways for endotoxin biosynthesis were elevated in abundance. Increased consumption of dietary fibre by approximately 40 g d^{-1} favourably remodelled these communities (characterized by increased acetate production from carbohydrate fermentation). Furthermore, the dietary intervention significantly reduced body weight, serum antigen load, and improved systemic inflammation in both groups. Additionally, patients with PWS showed improvements in hyperphagia-related behaviours (assessed by the *Dykens Hyperphagia Questionnaire*). Fermentation of dietary fibre by the gut bacteria produces short-chain fatty acids, which have been shown to increase the expression and secretion of anorexigenic hormones GLP-1 and PYY.[30] Additional studies are needed to determine whether modulation of the gut microbiota by dietary fibres would be a potential treatment strategy for excessive weight gain and hyperphagia associated with PWS. To help close this research gap, our research group led by Dr Andrea Haqq at the University of Alberta is currently evaluating the effects of high fibre supplementation on the gut microbiome profile, hyperphagia, and rate of weight gain in children with PWS (NCT04150991).[31]

Overall, current findings suggest that general advice on an energy-restricted, well-balanced diet higher in dietary fibres is recommended as the first-line approach in the dietary management of PWS. However, further research is needed to determine appropriate recommendations on diet composition within overall calorie limits in different age and disease stages to help patients with PWS achieve a healthy weight along with normal growth.

3.1.2 | Physical activity

Individuals with PWS engage in less physical activity than individuals with nonsyndromic obesity of similar BMI, which partially contributes to the low energy expenditure and development of obesity discussed above.[32,33] Factors such as low muscle mass and tone, poor coordination and cardiovascular fitness, and low stamina concentrations facilitate a more sedentary lifestyle.[32,34-36] Increased physical activity has therefore been recommended as coadjuvant therapies for the management of obesity in PWS, but the extent to which exercise promotes weight loss or changes in body composition is highly variable.[8]

All the studies investigating the acute and long-term responses to increased physical activity in individuals with PWS have recently been systematically reviewed; please refer to Morales et al for a detailed description of these studies.[37] Compared with controls with normal weight and obesity, children with PWS exhibited a similar hormonal response to a single session of resistance training but no significant changes in epinephrine and norepinephrine after an endurance training session. Of the eight studies identified that assessed the effects of increased long-term exercise interventions (duration ranging from 26 days to 6 months) on body weight, five reporting a reduction of 2% to 12% in body weight or 4% to 7% in BMI. The effects of long-term exercise on body composition were also explored; albeit, with mixed results. While three studies reported increases in muscle mass (2%-5%) after resistance exercise or home-based physical activity, one study using aerobic and resistance exercise showed a mean reduction of approximately 2.4 ± 1.3 kg and another study described no significant changes after home-based physical activity. With regard to fat mass, only two out of five studies described reductions in this body component after long-term exercise interventions. For instance, one study showed a significant decrease in body weight, BMI, and fat mass was conducted in youth with PWS who were asked to increase their moderate-to-vigorous physical activity through a home-based parent-led physical activity programme over 24 weeks.[38] The heterogeneous findings reported in this systematic review can be attributed to differences in the mode, frequency, duration, and intensity of the exercise interventions. It remains unclear whether the benefits of exercise can be sustained for a longer term in individuals with PWS. Furthermore, changes in body weight and composition obtained through physical activity and structured exercise in PWS are relatively small compared with other treatment regimens. Despite limited data, physical activity is recommended as an adjunctive therapy to maximize lean mass and efforts at body weight maintenance in PWS.

3.1.3 | GH replacement therapy

GH deficiency has been documented in a large number of children with PWS.[39] GH replacement therapy, the only Federal Drug Agency (FDA)-approved treatment specifically for PWS, has been shown to normalize linear growth and improve motor function, psychomotor development, and body composition in children and adults with PWS.[40] Specifically, GH treatment has been shown to decrease body fat and concomitantly increase lean muscle mass in children[41,42] and adults[43] with PWS. Mounting evidence suggests that continued GH therapy into adulthood increases muscle strength and exercise capacity in adult patients.[43] A study found that cessation of GH upon completion of linear growth was associated with worsened BMI and increased visceral adipose tissue in patients with PWS (aged 14.0-17.9 years).[44] As part of current standard of care for PWS, it is recommended that children with PWS begin GH therapy as soon as possible after genetic confirmation of the diagnosis of PWS.[39] After achievement of final height, long-term use of GH therapy in patients with PWS may be advisable to maintain optimal body composition.[44]

3.2 | Novel pharmacologic approaches

Current standard therapies have limited efficacy in ameliorating hyperphagia and progressive weight gain in PWS. There is broad consensus regarding the need to use pharmacological treatments when managing appetite and body weight in patients with PWS. The pharmacotherapeutic armamentarium for PWS is growing, and some of the drugs in the pipeline have shown promise for the treatment of PWS-associated hyperphagia and obesity (Table 1 and Figure 1).

3.2.1 | UAG analogue

Past studies have consistently documented that patients with PWS at all ages have high circulating levels of total ghrelin as compared with individuals with healthy weight and those with obesity.[72-77] Elevated ghrelin levels are thought to be involved in the pathogenesis of hyperphagia seen in PWS.[78] Two major forms of ghrelin are found in circulation, acylated ghrelin (AG) and unacylated ghrelin (UAG).[79] Recent evidence suggests that the ratio of AG to UAG is more relevant to hyperphagia in PWS than the absolute concentrations of total ghrelin.[79] A study measured all forms of circulating ghrelin and revealed that children and young adults with PWS had high circulating concentrations of AG.[79] Further, when compared with age-matched controls, patients without excessive weight gain or hyperphagia had a similar AG/UAG ratio, whereas those with abnormal weight gain and/or hyperphagia had a higher AG/UAG ratio. Seemingly, the switch to excessive weight gain in PWS coincided with the increase in the AG/UAG ratio.[79] This is in line with the results reported by previous researchers that obesity is associated with increased AG/UAG ratios.[80] Based on these findings, it was hypothesized that when UAG levels are too low for effective antagonism of the actions of increased

TABLE 1 Emerging pharmacotherapies for hyperphagia and obesity in PWS

Modality	Mechanism of Action	Development Phase	Advantages	Other Considerations
AZP-531	Decreases the appetite stimulating effects of AG; GHSR-independent suppression of lipogenic genes[45]	Phase 2b/3 underway	Potential to address PWS-specific increase in AG/UAG ratio; decrease adiposity in a GHSR-independent manner[46]	No long-term safety, efficacy data in PWS population yet
Oxytocin	Binds to G protein-coupled receptor, leading to the activation of several different second messenger systems that regulates appetite, emotions, and trust[47]	Phases 1 and 2	Potential to replace the relative deficit of oxytocin in patients with PWS, may have positive effects on hyperphagia and disruptive behaviours[48-52]	Complex and mixed clinical trial results; genetic variants, disease stage/age may be potential modulators of drug efficacy; need to determine the treatment period and dosing regimen
Carbetocin	Oxytocin analogue that selectively binds to G protein-coupled receptor, leading to the activation of several different second messenger systems that regulates appetite, emotions, and trust[47,53]	Phase 3 underway	Longer half-life than oxytocin; may bypass some medical complications or worsen behavioural symptoms caused by oxytocin; potentially useful for treating hyperphagia and behavioural symptoms of PWS[53]	No long-term safety, efficacy data in PWS population yet
Diazoxide (controlled release)	K^+-ATP channel agonist that may exert therapeutic effects through the down-regulation of insulin secretion, modulation of hypothalamic neuropeptide Y concentrations, increased of GABAnergic neuronal excitability, and/or the activation of KATP channels in adipocytes[54,55]	Phase 3 underway	FDA-approved drug for the treatment of hyperinsulinemia hypoglycaemia and acute hypertension; well-defined safety profile; potential to address hyperphagia[54]	No long-term safety, efficacy data in PWS population yet
Setmelanotide	Activates MC4R, which results in inhibition of food intake and stimulation of energy expenditure[56,57]	Phase 3 underway	May address underlying defect in hunger circuits[58]	No long-term safety, efficacy data in PWS population yet
Tesofensine and metoprolol combination	Tesofensine is a serotonin-noradrenaline-dopamine reuptake inhibitor[59,60]; metoprolol is a β-1 adrenergic receptor antagonist that counteracts the increase in heart rate and blood pressure induced by tesofensine alone[61]	Phase 2b underway	Potential to reduce appetite, decrease food craving, and increase fat utilization[62]	Possible exacerbation of already occurring behavioural problems and central nervous system disorders; no long-term safety, efficacy data in PWS population yet
Liraglutide	GLP-1 receptor agonist that delays gastric emptying and suppresses appetite[63,64]	Pilot studies in PWS	FDA-approved treatment option for chronic weight management[64]	No available data from randomized, double-blind, placebo-controlled clinical trials in patients with PWS
Exenatide	GLP-1 receptor agonist that delays gastric emptying and suppresses appetite[63,65]	Pilot studies in PWS	FDA-approved as immediate release and longer-acting extended release formulations for the treatment of T2DM[66]	No available data from randomized, double-blind, placebo-controlled clinical trials in patients with PWS; safety and efficacy of the once-weekly formulation has not been studied in PWS

(Continues)

TABLE 1 (Continued)

Modality	Mechanism of Action	Development Phase	Advantages	Other Considerations
GLWL 01 (orally available GOAT inhibitor)	Inhibitor of enzyme that catalyses ghrelin octanoylation, resulting in reduced production of AG and increased levels of UAG[67]	Phase 2	May modify food intake and prevent weight gain[68]	No available data from randomized, double-blind, placebo-controlled clinical trials in patients with PWS
RM-853 (orally available GOAT inhibitor)	Inhibitor of enzyme that catalyses ghrelin octanoylation, resulting in reduced production of AG and increased levels of UAG[67]	Preclinical	May modify food intake and prevent weight gain[68]	Early stage of development
JD5037 (peripherally restricted CB1R antagonist)	Peripherally restricted CB1R antagonist that targets the overstimulated endocannabinoid system in PWS to reduce appetite and body weight[69,70]	Preclinical	Potential to manage obesity-related metabolic disorders without producing adverse central nervous system effects[71]	Early stage of development; not clear if lack of central nervous system effect would still permit the same therapeutic efficacy as globally acting CB1R antagonist

Note. The table only summarizes the drugs in preclinical and clinical development in PWS. These are experimental drugs, which should not be used outside of a carefully monitored clinical study.
Abbreviations: AG, acylated ghrelin; CB1R, cannabinoid type 1 receptors; FDA, Food and Drug Administration; GHSR, growth hormone secretagogue receptor; GLP-1, glucagon-like peptide-1; MC4R, melanocortin-4 receptor; PWS, Prader-Willi syndrome; T2DM, type 2 diabetes mellitus; UAG, unacylated ghrelin.

AG in patients with PWS, the resulting higher AG/UAG ratio induces or contributes to the development of hyperphagia and obesity.[79] Therefore, a valuable approach to treat hyperphagia and obesity in PWS might be pharmacological alteration of the AG/UAG ratio, through increase in UAG concentrations (the denominator). UAG administration serving to replace the relative deficit of UAG in patients appears to be a promising therapy for PWS.

Although it was initially considered as an artefact devoid of biological activity, UAG is now well recognized as a metabolically active peptide.[45] AG exerts its effects through the growth hormone secretagogue receptor type 1a (GHSR-1a). UAG does not bind to GHSR-1a[81] and does not antagonize AG-induced activation of GHSR-1a in vitro.[82] Interestingly, UAG was shown to modulate the expression of genes involved in glucose and lipid metabolism in mice with tissue-specific deletion of GHSR-1a from fat, muscle, and liver, pointing to a direct action of UAG on improving insulin sensitivity and metabolic profile.[45] In a GHSR-independent manner, UAG was shown to suppress lipogenic genes and consequently decrease adiposity in rats, suggesting that UAG may have anti-obesity effects.[83] Moreover, there is evidence showing that UAG has antagonistic effect on certain activities of AG.[80] Inhoff et al showed in rats that the activating effects of AG on nesfatin-1 immunoreactive neurons were significantly reduced by coadministered UAG, which suggests an involvement of central mechanisms underlying the antagonistic effects of UAG on AG activity.[84] This is consistent with work in mice by Asakawa et al, in which UAG induced reductions in food intake and gastric emptying rate by acting on the hypothalamus.[85] Broglio et al first demonstrated that UAG, when coadministered with AG, counterbalanced the influence of AG on insulin secretion and glucose metabolism in healthy young adult volunteers.[86] In an intervention study, UAG improved glycaemic control in adults with T2DM, and this improvement was likely due to the suppressive effect of UAG on plasma AG levels.[87] Altogether, these studies clearly suggest a potential clinical benefit of UAG administration in patients with relatively high levels of AG and also in those with UAG deficiency.

AZP-531, a cyclic 8 amino-acid peptide, is a stabilized UAG analogue with improved plasma stability and pharmacokinetic profile.[46] Interest in potential clinical application of AZP-531 in PWS has been growing in recent years. In a phase 2, randomized, double-blind, placebo-controlled trial, 47 patients (aged 12-50 years) suffering from PWS-associated hyperphagia received daily subcutaneous injections of AZP-531 or placebo (3 mg for 50-70 kg and 4 mg for >70 kg body weight) for 14 days.[46] AZP-531 treatment resulted in significantly improved mean total score (P = .04), the nine-item score (P = .01), and the severity domain score (P = .02) of the validated *Dykens Hyperphagia Questionnaire* compared with placebo. These changes were also supported by improvement of patient-reported feelings of appetite after breakfast (P = .0004) in the AZP-531-treated group, while no significant change versus baseline was observed in the placebo group (P = .10). AZP-531 treatment was further found to reduce waist circumference (P = .047) and fat mass (P = .046), but no significant changes were detected in body weight, circulating ghrelin, or the ratio of UAG to AG. In addition, AZP-531 treatment significantly reduced

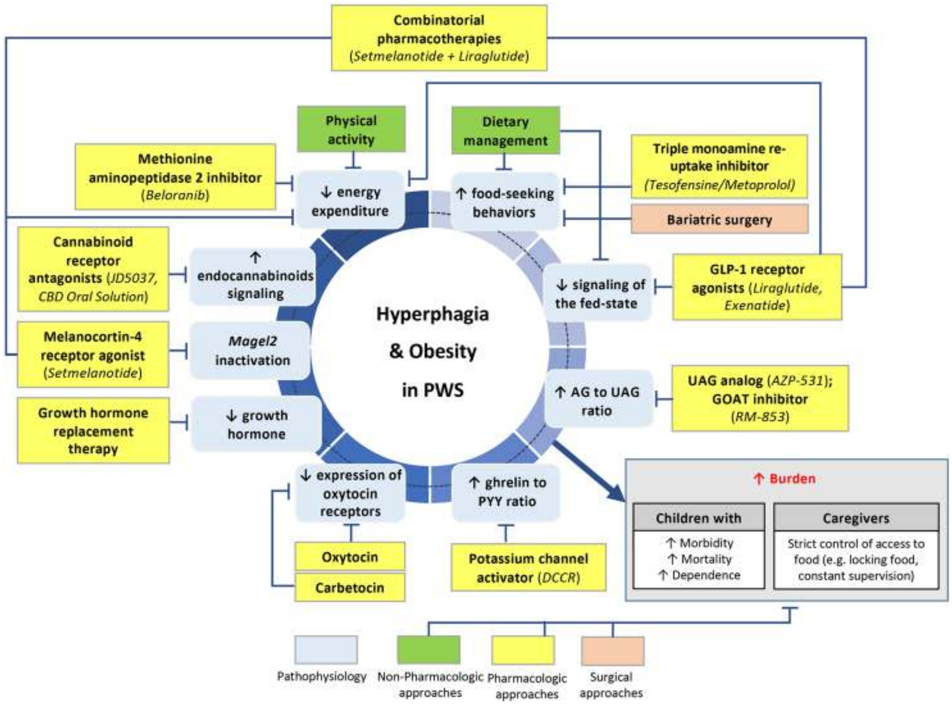

FIGURE 1 Summary of the mechanisms of action of current and emerging therapies for hyperphagia and obesity in Prader-Willi syndrome (PWS). The characteristic hyperphagia and obesity represent an increased burden for patients with PWS and their caregivers. Several mechanisms responsible for these clinical manifestations have been suggested, although their pathophysiology is not completely clear at the present. To curb the hyperphagia and obesity, emerging options of pharmacologic, nonpharmacologic, and surgical approaches are being studied in PWS. Each therapy targets different mechanisms of action to control these life-threatening conditions. Italic indicates drug name. AG, acylated ghrelin; AG, unacylated ghrelin; DCCR, diazoxide choline controlled release; GLP-1, glucagon-like peptide 1; GOAT, ghrelin *O*-acyltransferase; PYY, peptide YY

postprandial glucose levels in patients with PWS, which is consistent with observations in AZP-531-treated healthy individuals with overweight/obesity.[88] No serious adverse events were observed during the study, suggesting that AZP-531 may be well tolerated in individuals with PWS. The authors concluded that, based on current findings, longer-term treatments might improve body composition and metabolic parameters in patients with PWS. These overall results warrant further research on AZP-531 as a possible safe therapeutic drug in the treatment of hyperphagia in patients with PWS. In this study, multicentre collaboration resulted in a high rate of patient enrolment; its sample size was relatively large considering the rarity of PWS. However, while some participants were resident at home during the study period, other participants were resident at a PWS-dedicated hospital unit, introducing bias into the evaluation of the effect of AZP-531 on food-related behaviour.

Millendo Therapeutics, Inc (Ann Arbor, MI, USA) has recently initiated a two-part clinical study (NCT03790865) of AZP-531 with expected completion in March 2021.[89] The first part is a phase 2, 3-month, double-blind, placebo-controlled, dose-response study (60 or 120 mcg kg^{-1}) with a 9-month extension period. The second part is a phase 3, 6-month, double-blind, placebo-controlled trial with a 6-month extension period. Together, these studies will demonstrate the safety, tolerability, and effects of AZP-531 on hyperphagia and other food-related behaviours in patients with PWS. The study also will measure changes in fat mass, waist circumference, and body weight in patients with PWS and overweight/obesity.

3.3 | Oxytocin and carbetocin

Oxytocin (OXT) and its analogue, carbetocin, are extensively studied in PWS clinical trials and have shown potential for treating both hyperphagia and behaviour problems in PWS. OXT is a neuropeptide that plays a critical role in regulating a wide variety of human behaviours, such as maternal care, pair bonding, trust, and feeding.[90] A dysfunctional OXT system has been implicated in several behavioural disturbances including hyperphagia, social deficits, and increased anxiety, conditions common in PWS.[91] The number and volume of OXT-expressing neurons was found to be substantially reduced in the hypothalamus of individuals with PWS.[92] A whole genome microarray analysis also reported significantly attenuated expression of the OXT receptor gene in lymphoblasts from patients with PWS.[93] Exogenous OXT may exert therapeutic effects by binding to the OXT receptors (a G protein-coupled receptor), which activates Ca^{2+} channels and its downstream signalling cascades (including protein kinase C, Ca^{2+}/calmodulin-dependent kinase II, calcium/calmodulin-dependent protein kinase type IV, and calcineurin) that regulates appetite, emotions, and trust.[47] Preclinical treatments with OXT using animal models have yielded promising results. In mice with hyperphagic obesity, OXT replacement normalized food intake and decreased weight gain.[94] These research findings have sparked researchers' interest in the therapeutic potential of OXT in PWS.

The first published human study assessing OXT administration in individuals with PWS was carried out by Tauber et al. This double-blind, randomized, placebo-controlled trial aimed to evaluate the effects of OXT on adult patients with PWS (n = 24; aged 18-43 years).[48] Patients who received a single intranasal administration of 24 international units (IU) of OXT showed significantly higher trust ($P = .02$) in others, fewer sadness tendencies ($P = .02$), and less disruptive behaviours ($P = .03$) than did patients who received the placebo; maximum effects were seen 2 days following administration. However, the study observed no significant difference between the two groups in scores assessing eating behaviour. Einfeld et al conducted a similar crossover trial using OXT nasal spray in adolescents and adults (n = 22; aged 12-30 years) with PWS, in which participants received 8 weeks of either OXT or placebo separated by a ≥2-week washout period.[49] Adolescent patients were randomized to receive either 18 or 32 IU twice daily of OXT, while adult patients received either 32 or 40 IU twice daily. In contrast to the previous study, no significant difference between placebo and OXT groups was detected for any measure assessed, including hyperphagia/pica, temper outbursts, and weight.

More recently, Miller et al conducted a double-blind, randomized, placebo-controlled, crossover study in children with PWS aged between 5 and 11 years (n = 24).[50] These children received 5 days of 16 IU OXT daily and 5 days of 16 IU placebo daily with a 4-week washout period. Although, no significant changes detected in vital signs, appetite-related hormones, or weight, the short-term treatment with OXT was safe and well tolerated in children with PWS. Contrary to previous findings, Kuppens et al reported that OXT treatment had beneficial effects on social and food-related behaviours in children with PWS.[51] A double-blind, randomized, placebo-controlled, crossover trial was performed in 25 children with PWS aged between 6 and 14 years. Stratification by sex and age (6-10.99 or 11-14.99 years) was done, and the dose used was calculated according to the body surface (range 12-24 IU twice daily). Participants received either OXT or placebo for 4 weeks followed by the alternate treatment for another 4 weeks with no washout period. Intranasal OXT administration was shown to significantly reduce anger ($P = .001$), sadness ($P = .005$), conflicts ($P = .010$), and food-related behaviour ($P = .011$) and improve social functioning ($P = .018$) compared with placebo in children younger than 11 years of age (n = 17), but not in those older than 11 years of age (n = 8). To evaluate the effects of early OXT administration, Tauber and colleagues treated 18 infants (<6 months old) with PWS with 4 IU of OXT either every other day, daily, or twice daily over 7 days.[52] This treatment restored normal suckling activity and improved swallowing and social skills in treated infants and was well tolerated. Currently, a phase 2 randomized, double-blind trial of intranasal OXT is ongoing with expected completion in August 2020 (NCT03197662).[95] This study will measure the changes in eating behaviours, repetitive behaviours, weight and body composition, quality of life, and salivary OXT and hormone levels in 50 subjects with PWS (aged 5-17 years) following an 8-week intranasal OXT treatment. These results will aid in determining if OXT is an effective treatment for hyperphagia and other behavioural symptoms of PWS.

OXT and its closely related peptide, arginine vasopressin (AVP), are partial agonists of their homologous receptors.[96] High doses of intranasal OXT may saturate the OXT receptors and bind to the AVP receptors. AVP is anxiogenic; thus, increased binding of OXT to the AVP receptors may result in emotional responses and anxiety, manifested as temper tantrums.[50] Carbetocin, a synthetic OXT analogue, is an OXT receptor-selective compound, which would permit avoidance of AVP-receptor mediated complications of OXT, but potentially could accentuate OXT receptor-mediated side effects OXT receptor agonism. Carbetocin is generally well tolerated with a good safety profile and a longer half-life than that of OXT.[97] A phase 2 clinical trial evaluated whether intranasal carbetocin had a positive impact on hyperphagia in adolescents with PWS.[53] It was a prospective, randomized, double-blinded study carried out with 37 participants aged 10-18 years: 17 were randomly allocated to treatment and 20 to placebo (9.6 mg per dose, three times daily for 14 days). Treatment with intranasal carbetocin significantly reduced hyperphagia at the end of intervention compared with placebo ($P = .03$). It also reduced compulsivity and improved overall functioning ($P = .001$) without adverse effects reported. Although the specific mechanisms by which this may occur are not yet clear and the longer-term effects of carbetocin in PWS remain unknown, initial findings are promising. Results of this study demonstrate that carbetocin has therapeutic potential in treating hyperphagia and behavioural problems associated with PWS. Moreover, a phase 3, randomized, double-blind, placebo-controlled trial of intranasal carbetocin has commenced since November 2018 (NCT03649477).[98] The study is designed to examine the effects of intranasal carbetocin on hyperphagia, obsessive compulsive behaviours, and anxiety in PWS. An 8-week placebo-controlled period will be followed by 56 weeks of open-label treatment to obtain long-term safety and efficacy data for carbetocin use in PWS.

In summary, OXT and its analogue, carbetocin, seem to be well tolerated in patients with PWS, with little to no reported adverse effects. Future investigations should confirm the previous study findings with extended follow-up periods within larger, well-defined clinical cohorts and also determine long-term effects and safety.

3.3.1 | Potassium channel activator

Diazoxide is a K^+-ATP channel agonist approved for the treatment of hyperinsulinemia hypoglycaemia and acute hypertension. Diazoxide may exert therapeutic effects on PWS through the down-regulation of insulin secretion from pancreatic β-cells, the modulation of hypothalamic neuropeptide Y concentrations, the increase of excitability of the GABAnergic neuron, and/or the activation of K_{ATP} channels in adipocytes.[54] The effect of chronic diazoxide treatment on fat mass and metabolism was recently examined in mice with high-fat diet-induced obesity and inactivation of *Magel2*, a gene also inactivated in PWS.[55] This study showed that a 12-week oral diazoxide administration reduced fat mass, decreased blood glucose, and improved endurance capacity in these *Magel2* knockout mice but less effectively than in wild-type mice suggesting only partial restoration of energy homeostasis with diazoxide treatment. In addition, a phase 1 clinical study (NCT02034071) showed that a controlled release form of the benzothiadiazine derivative diazoxide reduced appetite-related behaviours and lowered fat mass in children and adults with PWS (aged 10-22 years), indicating that diazoxide might be a suitable candidate for treating hyperphagia in PWS.[99]

Very recently, a new once-a-day formulation of diazoxide, diazoxide choline controlled release (DCCR), was evaluated in children and adults with PWS and overweight/obesity in a phase 2 study.[54] In this pilot trial, participants (aged 11-21 years) received a 10-week open-label, dose-escalation treatment with DCCR, which was followed by a 4-week double-blind, placebo-controlled treatment period. In a dose-dependent manner, treatment with DCCR was shown to significantly improve hyperphagia ($n = 11$, $P = .006$), lower the number of aggressive behaviours ($n = 10$, $P = .01$), reduce body fat mass ($n = 11$, $P = .02$), and increase lean body mass ($n = 11$, $P = .003$), with a corresponding decrease in waist circumference.[54] Adverse events, including peripheral oedema and transient increases in glucose, were reported. Although the impact of diazoxide on PWS-associated hyperphagia is still not very well understood, current evidence suggests that diazoxide deserves further research attention. A phase 3, randomized, double-blind, placebo-controlled study of DCCR is recruiting patients (NCT03440814).[100] The study will further evaluate the effects of DCCR on hyperphagia and body fat mass in children and adults with PWS.

3.3.2 | MC4R agonist

The melanocortin-4 receptor (MC4R), a seven-transmembrane domain G protein-coupled receptor, plays a seminal role in energy and body weight homeostasis.[101] The precursor protein, pro-opiomelanocortin (POMC), produces several bioactive peptides, including the melanocyte-stimulating hormones (MSHs), corticotrophin (ACTH), and β-endorphin. The MSHs and ACTH then bind to the extracellular G protein-coupled melanocortin receptors, one of which is MC4R.[102] MC4R activation stimulates energy expenditure and inhibits food intake, resulting in a negative energy balance and potentially lessening obesity.[103] MC4R variants are the most common monogenic cause of obesity, with a prevalence ranged from 1.74% to 2.45% in children with obesity.[104-107] *Magel2* is one of several genes typically inactivated in PWS. *Magel2*-deficient mice were found to have functionally defective POMC neurons and were responsive to pharmacological treatment with an MC4R agonist that bypasses this defect.[56,108] Patients with PWS may also be responsive to therapeutic activation of the MC4R, which provides the rationale for the treatment of obesity with setmelanotide in PWS. Setmelanotide (formerly known as RM-493) is a potent and selective MC4R agonist in development for the treatment of rare genetic disorders of obesity. It binds with high affinity to the human MC4R, resulting in efficient activation of MC4R.[56] Although in vitro receptor affinity and activity data show that setmelanotide also exhibits agonist activity at the MC1R, MC3R, and MC5R, much higher concentrations (at least 20-fold) of setmelanotide are needed for activation of other melanocortin receptors than for MC4R.[56] In 2017, setmelanotide entered phase 3 clinical trials in patients with obesity bearing MC4R mutations.[57] In a phase 2, randomized, double-blind, placebo-controlled pilot trial of setmelanotide (NCT02311673), patients with PWS (aged 16-65 years) treated with the highest dose and for the longest period of time experienced clinically meaningful weight loss despite only modest improvement in hyperphagia.[58] Setmelanotide may have potential in reducing PWS-associated hyperphagia, and its manufacturer, Rhythm Pharmaceuticals Inc (Boston, MA, US), plans to further evaluate it in the PWS population.

3.3.3 | GLP-1 receptor agonists

GLP-1 is a hormone primarily synthesized by the neuroendocrine L-cells of the ileum and colon and is released in response to food intake.[63] Abnormalities in the postprandial secretion of GLP-1 have been linked to the pathophysiology of obesity and T2DM.[63] As a potential strategy to enhance GLP-1 actions, a number of studies have investigated the metabolic effects of GLP-1 receptor agonists. Intravenously administered GLP-1 receptor agonists (eg, liraglutide and exenatide) have been shown to delay gastric emptying and suppress appetite, which results in clinically meaningful weight loss, with no apparent cardiovascular or psychiatric adverse effects.[63,65,109,110]

Liraglutide, which shares 97% structural homology with human GLP-1, is an FDA-approved GLP-1 receptor agonist for obesity treatment. Liraglutide has a plasma half-life of 13 hours after subcutaneous administration, which allows for once-daily dosing without compromising therapeutic efficacy.[64] Data from phase 3, randomized, placebo-controlled trials show that liraglutide therapy, when paired with diet and physical activity management, effectively induced and sustained weight loss in patients with obesity,[111] supporting the efficacy of liraglutide as a weight loss agent. Senda et al was the first to report the benefits of liraglutide therapy in PWS.[112] In a case study, a 25-year-old female patient with PWS and hyperglycaemia received 1-year liraglutide monotherapy, which substantially improved her haemoglobin A1c (HbA1c) level (12.6%-6.1%), steadily decreased her BMI (39.1-35.7 kg m^{-2}) and effectively controlled hyperphagia. They also observed reductions in visceral fat area (150.1-113.2 cm^2), plasma active GLP-1 (2.1-1.2 fmol L^{-1}) and active ghrelin (137.0-27.7 pmol L^{-1}), and an elevation in insulin (108.1-277.0 pmol L^{-1}).

Exenatide, a GLP-1 receptor agonist that retains 53% sequence homology to native GLP-1, is a FDA-approved adjunctive treatment of T2DM in adults.[65,66] Exenatide has been shown to exert effects on reducing food intake and body weight in animals and adults with obesity with and without T2DM. Seetho et al reported in a case study that, after 1-year of exenatide therapy, a 19-year-old female with

PWS, T2DM, and significant morbid obesity exhibited reduced food intake and body weight decreased from 127.8 to 94.4 kg.[113] Sze et al further showed that a single injection of 10 μg exenatide was effective in increasing satiety after a meal in adult patients with PWS.[114] Exenatide use did not affect circulating total ghrelin levels in participants but markedly suppressed postprandial total circulating GLP-1 and PYY; apparently, the stimulated satiety was not mediated by these appetite hormones.

Salehi et al conducted the first longitudinal investigation of exenatide in patients with PWS.[115] In an open-label, nonrandomized trial, 10 adolescents and young adults with PWS and overweight/obesity (aged 14.7-24.6 years) received 6 months of exenatide treatment. Significant decreases were observed over time in total appetite scores (P = .004), specifically in the behaviour and drive categories. However, the treatment had no effect on weight or BMI. No significant change was seen in AG or pancreatic polypeptide (PP) despite a decrease in appetite scores; hence, the appetite-suppressing benefit could not be explained by exenatide's effects on endogenous appetite hormones. This finding agrees with the previous reports that the appetite-suppressing effect of exenatide is independent of appetite hormones. In fact, a study that investigated the mechanisms by which GLP-1 receptor agonists cause weight loss showed that intravenous exenatide decreased brain responses to food pictures in appetite- and reward-related brain regions in patients with T2DM and subjects with obesity.[116] Salehi et al further found no evidence of safety concerns with exenatide use, which suggests that chronic exenatide treatment may be well tolerated in patients with PWS. However, this study presented a number of important limitations such as lack of randomization, no blinding, no placebo-control, small sample size, and short duration of follow-up, which questions the quality of the findings.

The use of GLP-1 receptor agonists has also been evaluated in patients with hypothalamic obesity (HO). HO is a complex neuroendocrine disorder caused by hypothalamic damage and characterized by significant hyperphagia, lack of satiety, and rapid weight gain.[117] The mesolimbic area of the brain (ventral tegmental area and nucleus accumbens), which is the location of food reward centre, remains intact in patients with HO. Theoretically, pharmacological stimulation of GLP-1 pathway may suppress dopamine signalling and subsequently reduce consumption of highly palatable foods.[117] Zoicas et al showed that patients with HO who were treated with either liraglutide (n = 1) or exenatide (n = 8) lost 13 kg of body weight on average, and the weight loss was maintained over 6 to 44 months.[118] In other case reports of the efficacy of GLP-1 receptor agonists in HO, substantial and sustained weight loss was also observed in patients.[119,120] These overall results suggest that GLP-1 receptor agonists may enhance the hypothalamic input of the satiety signal and thus appears to be an important therapeutic option in patients with HO and obesity.

In summary, investigations regarding the safety and beneficial effects of GLP-1 receptor agonists in PWS are very limited, and no conclusions can be made at this time. However, results from case studies of PWS encourage future clinical trials of GLP-1 receptor agonists to explore whether the demonstrated suppressed appetite will reduce long-term food intake with subsequent weight loss in PWS. Liraglutide is currently being trialled in PWS by many research groups worldwide, and the research team led by Professor Paul Hofman at the University of Auckland has observed significant weight loss in their paediatric patients (NCT02527200).[121] The advent of a potent oral formulation of the GLP-1 receptor agonist setmelanotide which was recently FDA approved for patients with T2DM offers additional promise.[122]

3.3.4 | GOAT inhibitor

Ghrelin *O*-acyltransferase (GOAT) is an enzyme that catalyses ghrelin octanoylation, which is essential for ghrelin to bind and activate the GHSR-1a.[123] Studies using GOAT knockout mouse models demonstrated the absence of AG in blood and significantly higher levels of UAG relative to wild-type littermates.[124,125] Therefore, presumably, inhibition of GOAT would impede the production of AG and, as a result, suppress its acylation-dependent orexigenic and adipogenic effects, and this blockage would also increase the levels of UAG. Ghrelin is the only protein known to be octanoylated, which means that inhibiting GOAT is unlikely to have side effects owing to interference with other acylating enzymes.[126] As such, modulation of ghrelin signalling through GOAT inhibition presents a potential therapeutic avenue for treating obesity and T2DM.[67] Structure-activity analyses of ghrelin binding to GOAT have facilitated the development and optimization of GOAT inhibitors.[127] In animal models of Siberian hamsters and rats, treatment with GOAT inhibitor induced reductions in food intake.[128,129] GLWL Research Inc (Montreal, QC, Canada) has recently completed a phase 2 trial of GLWL 01 (NCT03274856), in which the efficacy, safety, and pharmacokinetics of this orally available GOAT inhibitor has been evaluated for treating hyperphagia in patients with PWS (aged 16-65 years).[130] Another investigational GOAT inhibitor, RM-853, is currently in preclinical development for PWS. Preliminary research of RM-853 reported a favourable pharmacokinetic, pharmacodynamic, and safety profile. In addition, this new class GOAT inhibitor prevented body weight gain and reduced fat mass in high fat-fed mice.[68] Its manufacturer, Rhythm Pharmaceuticals, plans to file an investigational new drug application with the US FDA in the first quarter of 2020.[68] Overall, inhibition of GOAT deserves further investigation as a novel strategy for treatment of obesity in PWS.

3.3.5 | Cannabinoid receptor antagonists

The endocannabinoid (eCB) system plays crucial roles in the regulation of appetite, body weight, and metabolism.[71] Cannabinoid type 1 receptors (CB1R), an important element of this system, are expressed most densely in the brain but are also present at functionally relevant levels in many peripheral tissues.[69] Research has shown that activation of CB1R increases appetite, insulin resistance, and hepatic lipogenesis,[69] whereas blockade of peripheral CB1R ameliorates obesity and its metabolic consequences.[70] Chronic treatment with rimonabant, the first globally acting CB1R antagonist, has been shown to reduce body weight and improve cardiometabolic risk factors in rats with obesity[131] and humans with overweight/obesity.[132-134] Although this drug was quickly withdrawn due to neuropsychiatric side effects mediated by the blockade of CB1R in the central nervous system, its successful use for weight loss clearly demonstrated that CB1R could be a promising approach in the treatment of obesity once this side effect is eliminated.

This has led to the development of peripherally restricted CB1R antagonists, which may have the potential to manage obesity-related metabolic disorders without producing adverse central nervous system effects. JD5037, for example, is a novel drug candidate acting as a peripherally restricted antagonist at CB1R. In a mouse model, JD5037 was shown to be of similar efficacy to rimonabant in reducing appetite, body weight, hepatic steatosis, and insulin resistance.[135] JD5037 reversed diet-induced hyperleptinemia and restored leptin sensitivity in mice with obesity. This leptin resensitization was shown to be significantly correlated with the reductions in food intake and body weight, suggesting that JD5037 might exert its hypophagic and weight-lowering effects via the reversal of leptin resistance. A similar study showed consistent anti-obesity effects of JD5037 in a PWS mouse model, in which mice receiving 28-day treatment with JD5037 displayed improvements in body weight, hyperphagia, and obesity-associated metabolic parameters.[71] The same study reported that there were increased concentrations of eCBs and CB1R in the hypothalamus of mice with PWS. These elevations were associated with increased fat mass, reduced energy expenditure, and decreased voluntary activity observed in mouse models of PWS. The dysregulated eCB system identified in mouse models of PWS was further confirmed in humans; there were upregulated levels of 2-arachidonoylglycerol and arachidonic acid in plasma of patients with PWS.[71] Thus, eCB system dysregulation may be responsible, at least in part, for the hyperphagia and obesity of PWS. Therefore, treatment with JD5037 may be an effective strategy for the management of obesity in PWS as it can block the pathophysiological stimulation of CB1R caused by the increased availability of eCBs.

Cannabidiol (CBD) is a nonpsychoactive phytocannabinoid found in the cannabis plant, with well recognized therapeutic potential for neurological diseases and cancer.[136] in vitro data suggest that CBD is a high potency antagonist of CB1R and CB2R agonists.[137] Similar to the in vitro observations, a study in rats showed that CBD by itself had no clear impact on food intake but could prevent the hyperphagic effects induced by CB1R agonist (WIN55,212-2) or 5-HT1A receptor agonist (8-OH-DPAT), which supported its role as a possible food intake regulator.[138] A phase 2 clinical trial of CBD Oral Solution (NCT02844933), developed by INSYS Therapeutics (Phoenix, AZ, US), was initiated with expected completion in May 2020 and would have provided evidence on the effect of the CBD on hyperphagia-related behaviour and its long-term safety in children and adolescents with PWS.[139] However, this study was terminated due to declaration of bankruptcy by the company in June 2019.

3.3.6 | MetAP2 inhibitor

Beloranib is an irreversible inhibitor of methionine aminopeptidase 2 (MetAP2) that has been shown to significantly reduce food intake and body weight in animals and humans.[140-142] One suggestion is that inhibition of MetAP2 suppresses endothelial cell proliferation, which would prevent adipose tissue expansion and thus obesity.[143] McCandless et al provided encouraging results concerning beloranib's beneficial effects on hyperphagia and body weight in patients with PWS (aged 12-65 years).[144] In their randomized, double-blind, placebo-controlled trial, patients who received beloranib at 1.8 and 2.4 mg d^{-1} had decreased total hyperphagia score, significant weight loss, and improved metabolic parameters compared with placebo. However, an unexpected study finding was excess blood clot formation, with two fatal events of pulmonary embolism in beloranib-treated participants leading to early study termination. Beloranib treatment is clearly unacceptable for further use in the PWS population. Nevertheless, these clinical trial results have demonstrated the potential of using a similar drug to treat hyperphagia and obesity in PWS and guided the development of newer MetAP2 inhibitors. ZGN-1061, for instance, is a novel MetAP2 inhibitor being investigated for treatment of diabetes and obesity; however, this drug is currently on clinical hold by the FDA.

3.3.7 | Other pharmacotherapies

Tesofensine/metoprolol, developed by Saniona (Ballerup, DK), are being evaluated in PWS. Tesofensine is a triple monoamine reuptake inhibitor with anti-obesity effects,[59,60] and metoprolol is a β-blocker used to counteract the adverse effects of increased heart rate and blood pressure induced by tesofensine alone.[61] Animal[145,146] and clinical trials[59,147] of tesofensine showed that it is well tolerated and highly effective in controlling appetite and producing weight loss in patients with obesity. Recently, a phase 2 clinical trial of tesofensine/metoprolol in PWS (NCT03149445) reported that patients (aged 18-30 years) treated with 0.5 mg tesofensine/50 mg metoprolol daily achieved a significant weight loss of 4.8 kg ($n = 5$) after 8 weeks and 7.9 kg ($n = 2$) after 13 weeks relative to placebo.[62] There was also a remarkable reduction in the total hyperphagia score, from 10 ($n = 6$) at baseline to 1 ($n = 5$) after 8 weeks and to 0 ($n = 2$) after 13 weeks. Adverse events such as an exacerbation of already occurring behavioural problems and central nervous system disorders occurred were reported in all participants. Interestingly, plasma levels of tesofensine and metoprolol in patients with PWS were higher compared with control subjects with obesity, which was at least partially due to the relatively higher fat percentage and lower metabolic rate in PWS. Therefore, in the second part of the study, lower doses of 0.125 mg d^{-1} were used to study the effects of tesofensine/metoprolol on body weight and eating behaviours in adolescents with PWS ($n = 9$; aged 12-17 years); although significant effects were not detected. Saniona started a 3-month open-label extension study with an increased dose of 0.25-mg tesofensine/metoprolol per day. Data from the trial showed acceptable tolerability and safety outcomes, as well as long elimination half-life of tesofensine/metoprolol in adolescent patients, which is similar to that in adult patients. However, no significant improvement in hyperphagia was found while an increase in body weight was detected in both tesofensine/metoprolol and placebo groups. Saniona is now seeking to establish the optimal dosing regimen in the adolescent population. Nevertheless, the positive results from the first part of the study suggest that tesofensine/metoprolol may have potential to induce clinically meaningful reductions in body weight and hyperphagia in patients with PWS, supporting its further clinical development as a novel pharmacological therapy for PWS.

The biological circuits regulating energy homeostasis have built-in redundancies, overlap considerably with other physiological functions, and are influenced by behavioural, social, and psychological factors, making them resistant to single perturbations.[110] By simultaneously targeting multiple components of these circuits, combination therapies may offer greater therapeutic benefits than individual treatments. For instance, several synthetic GLP-1 analogues have been employed to modulate the GLP-1 system for the treatment of T2DM and obesity. However, human studies assessing the effects of GLP-1 receptor agonists showed clinically relevant but only modest reduction in body weight.[148,149] In addition, GLP-1 receptor agonists are associated with dose-dependent adverse gastrointestinal effects, such as nausea, vomiting, and diarrhoea. These side effects limit the maximal metabolic efficacy that can be achieved by activation of GLP-1 receptor signalling and, at least partly, lead to decreased patient satisfaction and compliance with therapy.[150] Mono-agonism of the GLP-1 receptor has been further reported to have limited weight-lowering potential in clinical application.[151] Combination therapy that incorporates a GLP-1 receptor agonist with another pharmacological entity has been demonstrated as an effective approach to enhance the therapeutic utility of GLP-1. A combination of setmelanotide and liraglutide was reported to have an additive effect compared with administration of either agent as monotherapies in mice with diet-induced obesity.[152] The glycaemic and anorectic actions of both agents, along with the ability of setmelanotide to increase energy expenditure resulted in reduced body weight and enhanced glycaemic control and cholesterol metabolism, superior to what were achieved by corresponding monotherapies. Interestingly, codosing with MC4R and GLP-1 receptor agonist was found to enhance expression of each receptor, which may partially explain the mechanism of such additivity.

3.4 | Surgical approaches

3.4.1 | Bariatric surgery

Although bariatric surgery is currently the most effective therapy to induce weight loss in patients with morbid obesity, its use in PWS remains controversial. As previously reviewed by Scheimann et al,[153] various bariatric techniques, including truncal vagotomy, gastroplasty, endoscopic balloon placement, and malabsorptive procedures, did not have favourable outcomes in patients with PWS. However, more recently, Alqahtani et al reported some encouraging findings that laparoscopic sleeve gastrectomy (LSG) resulted in the reduction of body weight and resolution of comorbidities in patients with PWS (n = 24) compared with controls matched for age, sex, and BMI (n = 72).[154] The patients with PWS were untreated with GH, aged between 4 to 18 years, with a mean preoperative BMI of 46.2 ± 12.2 kg m^{-2}, which was equivalent to that of the control group (46.2 ± 11.7 kg m^{-2}). Within the first year after surgery, patients with and without PWS had similar weight loss (59.7 ± 18.7 in PWS vs 61.7 ± 14.4 in controls [P = 0.7]) of approximately 60% of their excess weight. No significant difference was found in postoperative BMI change and growth between the two groups. Additionally, in the PWS group, it was noted that a majority of comorbidities, including obstructive sleep apnoea (OSA), dyslipidaemia, hypertension, and diabetes mellitus, improved or were in remission post-operatively. No surgery-associated complications occurred, and no mortality or major morbidity was observed over the 5-year follow-up period. After the surgery, patients with PWS had better control of hyperphagia and food-seeking behaviours as reported by their families. The improvement was similar to the observation by Fong et al of two patients undergoing LSG and one undergoing laparoscopic minigastric bypass (LMGBP) (aged 15-23 years; preoperation BMI was 44, 46, and 50 kg m^{-2}, respectively) who reported decreased food cravings after surgery.[155] These patients had a mean weight loss of 32.5 kg, and their percentage of excess weight loss was 63.2 % within 2 years post-operatively. Additionally, the average fasting ghrelin level decreased from 1134.2 pg mL^{-1} preoperatively to 519.8 pg mL^{-1} 1 year post-operatively, and this reduction was observed in both LSG and LMGBP procedures. Fewer episodes of food-seeking behaviour in patients with PWS after surgery might be attributed to surgery-induced hormonal modulation. In this small cohort, no major perioperative complications or mortality occurred, though LSG gave more favourable weight loss outcomes compared with LMGBP. Most recently, data from a 10-year observational study showed that surgically induced weight loss and comorbidity resolution were not sustainable in the long term in a small group of patients with PWS (n = 5; aged 15-23 years).[156] In contrast to Alqahtani's findings, this study showed that, following an initial improvement in T2DM and OSA in the first 2 years, patients experienced progressive worsening and symptom rebound after 4 to 5 years. In addition, bariatric surgeries, including LSG and gastric bypass, failed to delay or prevent new onset of obesity-related comorbid diseases, such as hypertension. This study also reported obesity-related premature death in one patient.

4 | CONCLUSIONS

Hyperphagia and progressive weight gain in PWS, often lead to severe obesity, metabolic dysfunction, cardiorespiratory difficulties, and premature death.[6] Limited understanding of the pathogenesis of hyperphagia and weight gain in PWS has hampered the development of other therapeutic approaches. As such, the prevention of obesity in PWS is primarily through physical activity and dietary management, including restricted access to food and energy-reduced diets. However, low muscle mass limits these individuals' ability to increase their energy expenditure through exercise and therefore may not be an appropriate therapy. Alternative to physical activity, research findings suggest that an energy-restricted, nutrient and specifically dietary fibre-dense diet is important for weight management and health promotion in PWS, although an optimal diet for individuals with PWS still needs to be determined.

Given the difficulty in obtaining and maintaining a healthy BMI with only dietary restriction, pharmacotherapies aimed at improving hyperphagia and inducing weight loss in PWS are urgently needed. New mechanistic insights into the cause of hyperphagia and weight gain in PWS have revealed an expanding list of molecular targets for novel pharmaceutical agents. Phases 2 and 3 studies have demonstrated the efficacy, safety, and tolerability of liraglutide and exenatide in the treatment of idiopathic obesity. However, there are many possible different pathophysiological mechanisms involved in the development and maintenance of PWS-associated obesity, and thus, these drugs need to be further evaluated in PWS. Promising agents like OXT and CBD are being investigated in patients with PWS in phase 2 studies. In addition, some phase 3 clinical trials are underway to assess the therapeutic effects of carbetocin, AZP-531, setmelanotide, and DCCR. RM-853 and JD5037 have shown their potential for the treatment of obesity in animal studies and certainly merit more systematic evaluation in PWS. Although preclinical and clinical studies show convincing evidence that beloranib, a MetAP2 inhibitor, is effective for reduction of food intake and body weight, this drug is no longer available because of safety concerns. Nonetheless, MetAP2 inhibition might be a therapeutic approach to treat obesity in PWS, and new MetAP2 compounds for PWS are in development.[157] Tesofensine/metoprolol has demonstrated its potential for the treatment of obesity in patients with PWS.

Further studies are warranted to explore additional combination therapies that might yield greater therapeutic utility in PWS. Several recently approved drugs, such as lorcaserin, Qsymia (combination of phentermine and topiramate), and CONTRAVE (combination of naltrexone and bupropion), may also be evaluated in PWS; they could potentially improve satiety or ameliorate obesity in individuals with PWS. Furthermore, combinatorial approaches appear to be necessary for sizeable improvements to reverse the progression of obesity. Preclinical reports on the utility of MC4R and GLP-1 receptor coagonists show promising results, suggesting that this coagonism may clinically outperform single GLP-1 receptor agonists. A growing number of GLP-1-based combination therapies for treating obesity are in development.[110] Drug combinations allow each constituent to be given at lower doses, which may have a favourable rather than unfavourable effect on their tolerability profile. However, it is important to remember that every agent added will result in additional side effects. The choice to initiate combination therapy must be considered in each individual case as it may yield untoward effects in some patients.

Drug development for PWS can be associated with considerable challenges, including incomplete understanding of disease pathophysiology, requirement for standardizing clinically meaningful outcome measures, and difficulties of recruiting a sufficiently powered sample to evaluate. To address these unique challenges, a patient registry platform, such as the Global PWS Registry,[158] with extensive input from patients, organizations, and experts in the field will be an effective tool in collecting the data needed to define the natural progression of PWS, which would inform and advance research towards effective treatments. Investigations are also being frequently done using multicentre designs to allow for larger sample sizes; for example, carbetocin, DCCR, and APZ-531 are now being studied in different sites across the globe. Vigilance to detail, comprehensive planning, and multidisciplinary collaboration will help reduce the variance and improve clinical trial quality. Because patients with PWS may be on GH therapy or drugs to manage behaviour problems, psychiatric illness, and complications of obesity, clinical trials in this population must tolerate concomitant drug use where possible.[159]

Enthusiasm for bariatric surgery as a potential treatment for PWS was initially dampened due to the disappointing results reported in early studies in patients with PWS. With the availability of new bariatric procedures, a few short-term case reports showed positive results, such as substantial weight loss and amelioration of comorbid conditions, without the occurrence of surgery-associated complications in patients with PWS who underwent bariatric surgery. After comparing different procedures, LSG seems to achieve better results than other surgical options in patients with PWS and deserves further evaluation in the PWS population. However, there is insufficient evidence bearing on long-term safety or effectiveness to recommend the use of bariatric surgery for patients with PWS at this time. Significant improvements in body weight do not necessarily lead to effective control of excess appetite drive and enhanced quality of life in patients with PWS. Current evidence supports the value of early diagnosis and multidisciplinary care, which may prevent severe early onset obesity in patients with PWS. More controlled bariatric surgery studies reporting long-term outcomes with sufficient patient follow-up are needed to confirm the durability of weight loss, resolution of comorbidities, long-term complications, and metabolic changes induced by various bariatric procedures in patients with PWS.

In summary, new treatment options are needed to curb the life-threatening drive to eat in PWS. Research into the pharmacotherapies for hyperphagia and obesity in PWS has made considerable progress over the past few years, and many new drugs are on the horizon. However, the supporting evidence base for these available pharmacologic therapies for PWS is not yet optimal. Further studies are needed to evaluate the clinical efficacy and safety profiles of these agents and determine their place in the treatment of patients with PWS. With the progress that we have made in our understanding of PWS, an effective treatment of hyperphagia and weight gain in PWS is an exciting prospect for the near future. Furthermore, PWS could be a model to study the genetic basis of human energy homeostasis and appetite regulation, which would facilitate better understanding of the genetic contributions to obesity. Such information could yield promising strategies for addressing the obesity epidemic.

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CONFLICT OF INTEREST

A.M.H. and J.C.H. are clinical trial investigators for a multisite research study on setmelanotide in rare genetic disorders associate obesity sponsored by Rhythm Pharmaceuticals.

AUTHOR CONTRIBUTIONS

A.M.H. oversaw this narrative review. C.E.O. generated the figure. Q.T. wrote the first draft of the manuscript, which all authors read, contributed to, and approved for submission.

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