

Treatment of hyperphagia and obesity in Prader–Willi syndrome

■ Charlotte Höybye^{1,2} , Janice Foster³ , Anthony P. Goldstone⁴ , Linda Gourash³ , Jennifer Miller⁵ & Maithé Tauber^{6,7} 

From the ¹Department of Endocrinology, Karolinska University Hospital, Stockholm, Sweden; ²Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden; ³The Pittsburgh Partnership, specialists in PWS, Pittsburgh, Pennsylvania, USA; ⁴PsychoNeuroEndocrinology Research Group, Division of Psychiatry, Department of Brain Sciences, Faculty of Medicine, Imperial College London, Hammersmith Hospital, London, UK; ⁵Department of Pediatrics, Division of Endocrinology, University of Florida, Gainesville, Florida, USA; ⁶Department of Pediatric Endocrinology, Hôpital des Enfants, CHU Toulouse, Toulouse, France; and ⁷INFINITY, INSERM U1291, Université de Toulouse, Toulouse, France

Abstract. Höybye C, Foster J, Goldstone AP, Gourash L, Miller J, Tauber M. Treatment of hyperphagia and obesity in Prader–Willi syndrome. *J Intern Med.* 2026;1–21.

Prader–Willi syndrome (PWS) is a rare, neurodevelopmental, multisystemic syndrome caused by lack of expression of paternal genes on chromosome 15q11.2–13. PWS is characterized by muscular hypotonia, abnormal body composition, hormone deficiencies, cognitive dysfunction and behavioural issues, including hyperphagia, increasing the risk of severe obesity. A single causative gene for hyperphagia has not been identified, and regulation of hunger and satiety is complex and multifactorial, making it difficult to identify a specific neuropeptide or hormone as the most important. Cornerstone treatments are a strict, controlled diet and regular physical activity. Several clinical trials with different pharmacological agents have been performed attempting to reduce or treat hyperphagia and obesity. However, many drug programmes have been discontinued

due to adverse events or not reaching endpoints. In this review, we have focused on phenomenology and management of hyperphagia, treatment with oxytocin (OT), glucagon-like-peptide-1 receptor agonists (GLP-1RA) and diazoxide choline. We conclude that controlled food access is crucial; managing expectations about food mitigates food-related behaviour; OT treatment of infants with PWS results in less severe hyperphagia at ages 3 and 4 years old; and that the effects of GLP-1RA on body weight seem modest. Studies of diazoxide choline extended-release (DCCR), the first approved treatment of hyperphagia in PWS, have shown promising results, particularly in managing severe hyperphagia, reducing fat mass and improving behavioural issues. Thus, although progress is being made in targeted pharmacological therapies to control hyperphagia, controlled food access remains crucial to prevent obesity but is not sufficient for management of food and behaviour.

Keywords: hyperphagia, obesity, Prader–Willi syndrome

Introduction

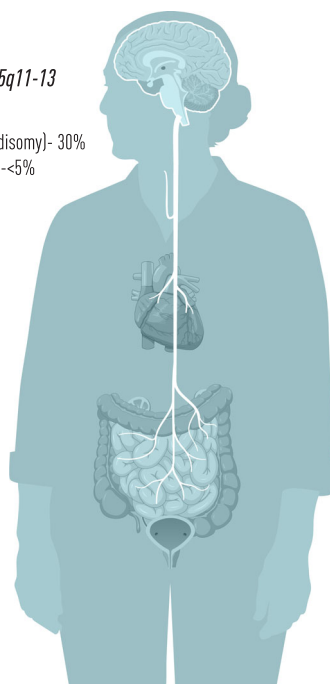
Prader–Willi syndrome (PWS) is a rare, neurodevelopmental, multisystemic syndrome. PWS occurs worldwide without any consistent geographic clustering [1]. The incidence is approximately 1/25,000 newborns, and males and females are affected equally [1]. PWS is caused by the absence of expression of specific genes on the paternally inherited chromosome 15 in the region q11.2–q13 [2]. The disorder is closely associated with genomic

imprinting, in which certain genes are expressed depending on whether they are inherited from the mother or the father. In individuals without PWS, several genes in the chromosome 15q11.2–13 region are active only on the paternal chromosome, whereas the corresponding maternal genes are naturally silenced through imprinting [2]. PWS can be caused by a paternal deletion (approximately 65%), a maternal uniparental disomy (UPD) (approximately 30%), or by an imprinting defect of the paternal chromosome region (<5%). The loss

Prader-Willi syndrome

Loss of paternal expression *Ch15q11-13*

-  Deletion - 65%
-  mUPD (maternal uniparental disomy) - 30%
-  ICD (imprinting center defect) - <5%



Neurodevelopment & behavior

Developmental & learning difficulties
Emotional & social dysregulation
Impaired behavioral control & judgment
Hypotonia & reduced pain sensitivity

Endocrine & hypothalamic dysfunction

Multiple hormone deficiencies
Abnormal growth & pubertal development
Sleep/wake & temperature dysregulation
Impaired hunger, thirst & satiety regulation
Altered stress responses

Autonomic & gastrointestinal dysfunction

Impaired suck-swallow-breathing coordination
Gastrointestinal dysmotility
Impaired bladder emptying
Reduced heart-rate variability
Low energy expenditure

Metabolic & obesity-related complications

Obesity & abnormal body composition
Glucose & lipid dysregulation
Metabolic syndrome
Sleep-disordered breathing
Increased morbidity & premature mortality

Fig. 1 Typical characteristics of Prader-Willi syndrome and associated risks and consequences.

of functioning paternal genes primarily affects the hypothalamus, leading to uncontrolled, excessive eating (hyperphagia), obesity, behavioural issues and hormone deficiencies. Several of the genes in the affected region of chromosome 15 have been studied, and each of them can be associated with one or several of the symptoms of PWS, but it has not been possible to relate all symptoms of PWS to a single causative gene, although animal studies of postnatal knockout of the *Snord116* gene cluster recapitulate the disease trajectory [3]. Furthermore, microdeletions involving the *SNORD116* gene cluster can produce many of the PWS phenotypes in humans, including hyperphagia and obesity [2]. PWS occurs sporadically, and no strong environmental causes have been identified [4]. However, advanced maternal age incurs an increased risk of maternal UPD subtype [4].

The clinical phenotype varies with age [2, 4]. In early infancy, PWS is characterized by severe hypotonia, poor appetite and feeding difficulties, followed in early childhood by excessive eating with a high risk of development of severe obesity unless food intake is supervised and restricted (Table 1 and Fig. 1). Motor and language development is

delayed, and most individuals with PWS have a mild to moderate intellectual disability with a typical IQ range between 50 and 70. However, the cognitive profile is uneven, with relative strength in visual processing and relative weaknesses in abstract reasoning, executive function and short-term memory. There are also differences related to the genetic subtype. Individuals with the deletion subtype have a more typical physical phenotype, lower IQ, more compulsive behaviours and skin picking [5]. In contrast, individuals with the maternal UPD have higher verbal cognitive ability and less typical facial features but a higher risk of autism in early childhood and affective psychosis in adolescence and adulthood [5]. Individuals with imprinting defects can be more mildly or atypically affected largely depending on the genes involved.

Hypogonadism and genital hypoplasia are very common in both genders [6]. Although precocious puberty may occur with incomplete evolution, puberty is incomplete or absent, and most are infertile. Without growth hormone (GH) treatment in childhood, stature is short. A distinctive behaviour with temper tantrums, stubbornness, difficulty changing routines and anxiety is typical.

Table 1. Age-related characteristics of Prader–Willi syndrome and their treatment.

	Infants, children and adolescents	Adults	Treatment
Physical features	Severe hypotonia (poor muscle tone) in infants; narrow forehead; almond-shaped eyes, small hands and feet	Dysmorphic features persist, but less prominent; obesity	Physiotherapy
Growth and endocrine	Failure to thrive in infancy; short stature; GH deficiency; hypogonadism; delayed/incomplete puberty	Short stature if untreated with GH in childhood; hypogonadism; infertility, reduced muscle mass; risk of osteoporosis	Replacement of hormone deficiencies (mostly GH and sex hormones)
Appetite, satiety and metabolism	Poor feeding in infancy, switching to hyperphagia at age 2–4 years; risk of rapid onset of obesity	Chronic hyperphagia; severe risk of obesity; Type 2 diabetes and metabolic syndrome	Speech and language therapist for sucking and swallowing disorders; strict supervision of food access; calorie-controlled diet; controlled food access; education of caregivers; treatment of comorbidities of obesity
Cognitive and developmental	Mild to moderate intellectual disability, delayed motor and language milestones, learning difficulties	Stable intellectual disability, executive function deficits, difficulty with independent living	Speech and occupational therapy; special educational services; supervised assisted living; vocational programmes
Behavioural and psychiatric issues	Temper tantrums, food-seeking behaviours, rigidity, stubbornness, skin picking; features of autistic disorder more frequent among infants and young children with mUPD; social disabilities; impaired emotion regulation	Persistent behavioural issues; obsessive–compulsive traits; increased risk of psychiatric illness; affective psychosis (60%) is more frequent among adolescents and adults with mUPD	Consistent routines; clear boundaries around food and matters of importance (salience); behavioural therapy; treatment of psychiatric illness
Other medical issues	Sleep disturbances; risk of sleep apnoea; scoliosis; thick saliva; reduced pain sensitivity	Obstructive sleep apnoea; daytime sleepiness; comorbidities to obesity	Treatment of medical issues and comorbidities

Abbreviations: GH, growth hormone; mUPD, maternal uniparental disomy.

Characteristic facial features, strabismus and scoliosis are often present.

Hyperphagia is the constant pathologic urge and preoccupation to find and consume food and a concomitant constant drive to eat that can advance into life-threatening food-seeking behaviour. Hyperphagia is a central feature of PWS and has a strong negative impact on education, personal interactions and relationships, occupational performance and quality of life [7]. It affects not only the individual with PWS but also the per-

son's caregivers. A study exploring caregivers' burden showed that PWS causes high caregiver burden and impacts most aspects of caregiver life [8]. The burden increases with the age of the individuals with PWS, reaching its highest levels in caregivers of adolescents and young adults [8].

Hyperphagia incurs a very high risk of developing obesity, and obesity is a primary phenotypic component of PWS [9]. The arcuate nucleus in the hypothalamus is of central importance for controlling metabolism, hunger and satiety.

Hypothalamic neuropeptides, such as neuropeptide Y (NPY), agouti-related protein (AgRP) and alpha-melanocyte stimulating hormone, as well as oxytocin (OT), orexin and tachykinins, are the most important neuropeptides produced within the central nervous system regulating hunger and satiety [3, 10]. Indeed, there is a smaller hypothalamus on structural neuroimaging in PWS compared to obesity-matched controls, which correlates with a higher body mass index, with hypothalamic structural connectivity associated with impaired satiety [11].

However, peripheral hormones such as insulin, leptin, ghrelin and glucagon-like peptide-1 (GLP-1) are important regulators [3]. In PWS, particularly the hunger hormone ghrelin has been of interest as plasma ghrelin concentrations on the group level are consistently high in PWS compared to typical individuals, though there could be defects in ghrelin processing confounding interpretation [3, 12]. Thus, the regulation of hunger and satiety is multifactorial, involving a complicated interplay between different factors, making it difficult to identify a specific neuropeptide or hormone as the most crucial in PWS [10].

The prevalence of obesity in individuals with PWS has been reported to be 40% in children and adolescents and 82%–98% in adults [13]. Body composition is abnormal, with more body fat than lean body mass, and compared to age, sex and BMI-matched controls, visceral adipose tissue is less in PWS, leading to fewer adverse metabolic consequences [14, 15]. In addition, individuals with PWS have significantly lower energy expenditure than controls, probably due to the lower lean mass, increased fat mass, GH deficiency, leptin resistance or inadequate fat oxidation [14].

Exercise and restricted calorie intake are vital for managing PWS. Exercise is important to counteract hypotonia and low muscle mass and has a positive effect on health, but the motivation for spontaneous physical activity in individuals with PWS is usually low [16, 17]. Studies of habitual physical activity in children with PWS have reported a positive association between lean body mass and improved muscle strength, walking distance and coordination, but without significant effect on weight and fat mass [18]. However, physical activity along with a restricted and externally controlled calorie intake consisting of 8–11 kcal/cm height/day can maintain weight in a healthy range

and prevent obesity [19, 20]. Repeated counselling by a dietician is important for all.

The knowledge of PWS and clinical management has improved considerably over recent decades. The approval of GH treatment in children with PWS since the year 2000 has led to a dramatic change in the phenotype, with normal adult height and improved psychomotor functioning and body composition [4], but GH has no effect on hyperphagia and is not a weight-reducing medication. Hyperphagia and obesity remain major issues for individuals with PWS attempting to live an independent life and for the increased risks of comorbidities and early death secondary to obesity [21]. The rate of mortality has been reported to be 15 times higher in PWS than in non-PWS, with a mean age at death of 42 years [22]. Improving life expectancy in PWS largely depends on managing both non-obesity and obesity-related consequences of hyperphagia through improved support and the development of new treatments for hyperphagia [21]. Several drugs have been developed or are in development for the treatment of obesity and hyperphagia in PWS [23, 24]. The present review will focus on phenomenology and management of hyperphagia and available pharmacological treatment of hyperphagia and obesity (GLP-1RA, OT and analogues and diazoxide choline).

Phenomenology and management of hyperphagia in PWS

PWS is a rare genetic disorder with a complicated phenotype that changes across development. It has been identified as a neuroendocrine disorder associated with hypothalamic obesity. One of the most interesting aspects of the PWS phenotype is the change from failure-to-thrive in infancy to increased interest in food around age 5 years followed by hyperphagia by age 8 years that leads to overweight/obesity unless access to food is controlled in the environment [25]. The nutritional phases of hyperphagia in PWS have been described and validated [26–28].

Although these stages have been delineated clinically for nearly 15 years, the neuroendocrine correlates of these stages are just now being identified. For example, during the transition from median ages 9–25 months, where feeding and appetite is improved and the child is growing appropriately (Phase 1b), to median ages 8 years to adulthood, where the individual becomes hyperphagic and

rarely feels full (Phase 3), a statistically significant rise in serum insulin level was identified among children with PWS corresponding to weight gain, hyperphagia, and overweight/obesity [29]. Further, although elevated fasting plasma ghrelin has been noted in infants long before the hyperphagia begins [30], it appears that it is the ratio of serum acylated to unacylated ghrelin (the unmodified form that decreases with age) correlates with the nutritional stages [31]. However, ghrelin shapes the *reward* for food and other preferences through its effects in the dopaminergic striatal system in the brain [32]. However, suppression of acylated ghrelin (AG) using somatostatin analogues or inhibition of the conversion of unacylated to AG using a pharmacological inhibitor of the ghrelin *O*-acyltransferase enzyme did not reduce hyperphagia or obesity in PWS [33].

There has been a myth among the clinical and scientific community that a hypothalamic ‘switch’ turns on ‘hunger’ resulting in hyperphagia in PWS. Parents are still being told that their children are constantly hungry, and they must deny food to maintain health and wellbeing [34]. It is now understood that hyperphagia is related to a satiety deficit that has been validated both by experiments on eating behaviour and brain imaging [35–37]. Our clinical experience has led to the hypothesis that the hypothalamic deficit in PWS that appears at birth is lifelong, and compared to controls, people with PWS of all ages have diminished satiety and possibly even diminished hunger. In addition, there is an altered thirst/quench signalling causing them to drink inadequately unless flavoured water is available, which then must be limited because they are capable of water intoxication, and the same is reported by parents and carers of adolescents and young adults, although idiopathic excessive water intake is rare [38, 39]. Therefore, it is our understanding that the maturation of reward pathways in the brain outside the hypothalamus may be responsible for the changes in food interest and eating (and drinking) behaviour across the nutritional stages. In fact, when comparing children with PWS and obesity to controls, similar decreases in cortical volume were found in brain regions associated with control of eating behaviour, even though children with PWS had lower grey matter volume in the hypothalamus and white matter abnormalities compared to children with obesity [40, 41].

The PWS Personality Questionnaire (PWSPQ) is a parent-informed questionnaire assessing six domains of the behavioural phenotype: food-related drive behaviours, non-food-related drive behaviours, cognitive rigidity, disruptive/impulsive behaviour, stress/mood symptoms and skin picking. Items are scored 0 (never present); 1 (present in the past); 2 (present currently) and 3 (present now and interfering with function). There are 20 items in the food-related domain. Using the PWSPQ, it was observed that mean scores for food-related drive behaviours increased after age 10 years, and the number of parents controlling food and drink access nearly doubled (Table S1) [42]. Preoccupation with food, eating too fast and manipulating, arguing or displaying tantrums to procure food are the most common behaviours. Approximately 10%–20% of individuals with PWS do not display hyperphagia, although all other domains of the phenotype are endorsed on the PWSPQ [42].

From a developmental perspective, there is evidence to suggest that food is not the only driving force behind the behavioural phenotype. In young children, both with and without PWS, repetitive questions about the ‘who, when and where’ aspects of the daily schedule alleviate anxiety about uncertainty. In young children with PWS, these repetitive questions appear *before* food questions. In most young children, when expectations are disappointed, a tantrum occurs. This reflects the typical maturation (myelination) of the orbitofrontal cortex that begins around age 2 years. It is important to realize that in the young child with PWS, food preoccupation does not drive repetitive questioning, and tantrums are not caused by the expectation for food.

Starting at age 4 years, typical children develop selective interests and preferences for activities, objects and people related to imagination, such as dinosaurs, animals, baby dolls and role play. Young children with PWS often develop interests in objects (pencils, papers, tissues or collectibles such as DVDs, Beanie Babies and YouTube videos) as well as activities associated with sensorimotor stimulation, such as overuse of lotions, liquid soaps, shampoos and excessively long showers. The emergence of these behaviours may be related to the maturation of the salience system in the anterior cingulate cortex, which is also

responsible for the development of egocentrism in typically and atypically developing children [43]. Typical children habituate to their desire for these preferred items, but children with PWS do not. Parents describe this phenomenon as '*enough is never enough*' [44]. In our experience, the progression of the maturation of the anticipation, reward, and salience systems in the brain is similar in both typical children and children with PWS. This maturation shapes behaviour outside the influence of the hypothalamus and applies to both food and non-food items.

Successful weight management of hyperphagia in PWS requires frequent monitoring of weight, limiting calorie intake, controlling food access and establishing food certainty and predictability. Because of low lean body mass and hypotonia, calorie needs may be 60%–80% of typical requirements [19, 20]. Although exercise is essential for pulmonary function, health and wellbeing, it is rarely adequate for the calorie expenditure necessary to offset energy intake.

Food security is the essential psychological construct for managing both weight and behaviour in PWS [45]. It is a foundational management concept, which was derived from clinical observations during thousands of hours of experience working with children, adolescents and adults with PWS hospitalized on an inpatient rehabilitation unit in Pittsburgh, PA, USA. Patients entered the programme with histories of relentless food seeking, uncontrolled weight gain and severe behaviour problems. Noticeable improvements in behaviour were almost immediate among patients without psychiatric comorbidity in the highly structured programme that provided predictability, consistency and non-contingent reinforcement.

Controlled food access is only one component of food security. Rather, psychological food security is summarized in three simple rules: **no doubt about** what, how much, and when food is going to be provided (visualized diet plan with portion control); **no chance** of getting food outside the diet plan (no opportunity); and **no disappointment** so that food-related behaviours are minimal (expectations are managed). Food-related behaviours—such as food seeking, food preoccupation, verbal requests for food and behavioural manipulation for food—will reappear with lapses in the protocol.

The Red/Yellow/Green (RYG) system was adapted from the Traffic Light Diet, developed in 1972 at the University of Pittsburgh by Leonard Epstein, PhD, who was studying weight loss in adolescents with obesity within a family behavioural treatment model [46]. The RYG system was taught to patients and their families and was published as a manual by the Ontario Prader-Willi Syndrome Association [47]. The color-coded food groups were easily assimilated by patients and accommodated family preferences. This shifted the locus of control of food management from the dietician to the patients' families. Although the system was initially implemented for calorie control and weight loss, it was associated with behavioural improvement [48].

Family dietary and behavioural training emphasize the importance of maintaining predictability (food security principles) even when goal weight has been achieved. Behavioural improvement is the result of managing stress and anxiety related to uncertainty about food, essentially 'putting a lock on the thought'. The concept of psychological food security was disseminated to families across the world through the DVD *Food Behaviour and Beyond* produced by the International PWS Organization (IPWSO) and PWSA-USA [45]. In essence, food security is the cognitive behavioural therapy for individuals with PWS.

In summary, hyperphagia is a *reward-seeking* behaviour uninhibited by satiety or behavioural habituation. In our opinion, the progression of the nutritional phases from failure-to-thrive to hyperphagia is associated with the developmental neuro-maturation of reward pathways in the brain. The prevailing paradigm has been that a developmental shift within the hypothalamus is the reason for the behavioural progression through the nutritional phases. However, an alternative view is that the neuroendocrine deficit in PWS is static, and the neurodevelopmental maturation of the reward network outside the hypothalamus explains behavioural changes in the nutritional stages. Controlled food access saves lives, but food security improves the quality of life.

Oxytocin treatment in PWS

More than 30 years ago, Swaab et al. [49] reported for the first time based on immunohistological studies of brains of people with PWS, a decrease in the number and volume of OT-producing neurons in the hypothalamic paraventricular nucleus

(PVN), without differences in arginine vasopressin (AVP) neurons compared with controls. Subsequently, Muscatelli et al. also reported abnormal OT neurons in the PVN in two so-called PWS mouse models obtained by inactivating *Necdin* and *Magel2* genes, two maternally imprinted genes of the PWS chromosomal region [50, 51]. Moreover, OT treatment of *Magel2* KO pups in the first 5 h of life was shown to rescue the high early lethality by restoring normal suckling of pups and normal behaviour in adults comprising learning, memory and social abilities [52]. These results are linked with normalization of the OT pathways comprising development and function of OT neurons and OT receptors [52].

OT is a neuropeptide secreted mostly by hypothalamic neurons in the PVN and supraoptic nuclei with axon projections in various parts of the brain and hindbrain. It acts by binding to a single type of receptor (OTR), which is widely expressed in the brain and at the periphery and has various transduction pathways and possible heterodimerization with other brain receptors. OT can also bind to central AVP receptors with a lower affinity. OTRs are present on PVN neurons, nucleus accumbens neurons, central amygdala neurons, dorsal motor nucleus of vagal nerve neurons and the ventral tegmental area neurons of the limbic system [53].

From a pathophysiological point of view, this abnormal OT pathway documented in PWS and mouse models is now considered to explain at least in part, the PWS phenotype with feeding and behavioural issues and the specific neurodevelopmental trajectory of the disorder [4].

OT was first identified as a neurohormone with peripheral effects controlling uterine contractions during delivery and then lactation in mammals. Synthetic OT has been largely used to induce labour and maintain lactation for more than 50 years [53]. More recently, OT is also considered as a neuropeptide with central effects, acting as a brain neuromodulator and involved in appetite control and behaviour, particularly favouring bonding and social interactions, and emotional regulation in tight links with the limbic reward circuit [53, 54]. OT, like AVP, is linked to the autonomic nervous system, which controls homeostasis such as body temperature, the cardiovascular system, oesophagus-gastrointestinal motility, fluid and electrolytes, and sleep [55].

Clinical trials in people with PWS started in 2009 with the first publication on 24 adults with PWS who received a single intranasal administration of 24 IU OT or placebo, followed by several studies detailed in Table S2 [56–63]. The objectives of the clinical trials were always to improve both feeding and behavioural problems, the two core symptoms of PWS, which are tightly linked and may be controlled by OT.

Early studies of intranasal OT showed mixed findings. In the randomized controlled trial (RCT) mentioned above, Tauber et al. reported no significant improvement in eating behaviour after a single OT administration in adults with PWS, although more participants in the OT group reported reduced hunger compared with placebo [56]. Subsequently, the larger crossover RCT conducted by Einfeld et al. in adolescents and adults found no significant effects on hyperphagia or behavioural outcomes after 8 weeks of treatment [57]. More encouraging results were observed in younger children. In a Dutch crossover study, Kuppens et al. found no overall effects on weight or BMI, but children younger than 11 years demonstrated significant improvements in food-related behaviour, emotional regulation and social functioning [58]. Likewise, Miller et al. reported reductions in hyperphagia, anxiety and repetitive behaviours following short-term OT treatment in children with PWS [59]. These findings were supported by Damen et al., who observed beneficial effects on social and eating behaviour, particularly in boys and in children with deletion subtypes [60]. In contrast, Hollander et al. found no significant improvements in hyperphagia or weight-related outcomes [61]. Clinical trials on carbetocin, a longer acting OTR agonist with higher selectivity for the OTR, have also been performed. In a Phase 2 trial of intranasal carbetocin, Dykens et al. demonstrated significant improvements in hyperphagia and behavioural symptoms in hyperphagic children and adolescents with PWS [62]. Furthermore, the larger Phase 3 study by Roof et al. observed no significant benefit of a higher dose regimen, whereas the lower dose regimen significantly improved hyperphagia as well as anxiousness and distress-related behaviours [63]. In a press release, the sponsor announced that the results of the recent Phase 3 study with the low dose of intranasal carbetocin for 12 weeks did not give positive results, but results are not yet available.

A metanalysis published in 2023 analysed 117 patients, with 56 patients receiving OT and 61 patients receiving placebo, and concluded that the overall effect of OT in people with PWS was insignificant [64]. Although the conclusion is based on the results of the above studies, it may not be fully correct; a more detailed and nuanced discussion is needed. Indeed, a considerable amount of evidence in the literature on OT treatment has identified the important role of various factors that may modulate the effects of OT, such as age, dose, sex, hormonal and social/environmental context which may act by epigenetic modifications [65]. Major differences exist between studies regarding the age of the patients, which ranges from 5 to 29 years. The OT system, including neuron development, secretion and OT receptors, varies with age, which may explain some differences observed in the studies and between them. As mentioned above, Kuppens et al. showed that children below 11 years are better responders regarding feeding and social behaviour, whereas adolescents do not show any positive changes, with some displaying increased anxiety [58]. Various effects of different doses are widely known in PWS. For example, patients with PWS seem to be very sensitive to treatments such as GH [66] and psychotropic treatments. This may be linked to the differences documented in cytosine methylation in genomic regions involved in drug-resistant pathways [67].

In addition, the OT dose used and the type of daily administration (once, twice or thrice a day), together with the duration of OT treatment, are widely different between the studies and may explain some discrepancies. In the study of Einfeld et al., the worsening effect on behaviour (tantrums) observed with the very high dose was by the authors possibly attributed to OT binding to the AVP receptors [57]. Although the OT half-life in plasma is short, its effects in the brain may last for a longer period. In addition, the binding of OT to the dendritic OT receptors located in the OT-secreting neurons can, in turn, increase the secretion of OT in a positive loop, thus amplifying the effect of exogenous OT [67, 68].

OT is a brain modulator with lasting and long-term effects via brain plasticity, which is not compatible with the cross-over design of most of the clinical trials shown in Table S2. Therefore, the placebo period after the OT treatment period is not equivalent to the placebo period prior to OT administration, and therefore these placebo groups should

not be merged as is classically done in cross-over design statistical analyses. In addition, the optimal duration of the washout period cannot be calculated and is possibly longer than that used in the clinical trials with a crossover design. Sex differences have been reported in the study of Damen et al., with males being better responders than females even in the prepubertal age, suggesting that it is not only related to sex steroids and may be related to differences in OT levels, which are lower in males [60].

Finally, one major point is the possible impact of genetics, as Damen et al. reported PWS patients with chromosome 15q11–13 deletion were significantly more sensitive to OT treatment [60]. Interestingly, a recent publication showed differences in plasma OT concentrations according to genetic subtypes, with lower OT in the deletion subgroup compared with the non-deletion subgroup, suggesting that deficits of OT may be greater in this population and substitution with low dose may be the appropriate treatment option [64]. In this article, the authors also showed that AVP levels are lower in the non-deletion subgroup of patients with PWS, suggesting that this group of patients may benefit from AVP treatment instead of OT treatment [69].

Lastly, given the results obtained with OT treatment, we also may hypothesize that early OT ‘priming’ in infants with PWS may be necessary to allow the best treatment effect at each age. Our publications on early OT treatment in infants with PWS have shown short- and long-term positive effects with a less severe disorder at 3 and 4 years [70, 71].

Glucagon-like peptide-1 receptor agonists in PWS

In non-PWS individuals, a series of Novo Nordisk sponsored placebo-controlled clinical trials (STEP programme) of the GLP-1 receptor agonists (GLP-1RA) semaglutide 2.4 mg once weekly dose for treatment of overweight/obesity have shown significant weight loss in adults and adolescents without Type 2 diabetes mellitus (T2DM) of 11.1%–19.3% over 48–68 weeks (compared to placebo), though weight loss is less in those with T2DM at 6.2% (compared to placebo), and there is weight regain after cessation of semaglutide [72–79].

In non-PWS individuals, semaglutide treatment reduces appetite and sweet and savoury food

cravings, increases satiety and improves food-craving control, which is correlated with weight loss [80, 81], and improves positive mood and obesity-related quality of life [82, 83]. GLP-1RAs including liraglutide, dulaglutide and semaglutide may also reduce the frequency of binge episodes in binge eating disorder [84–88], though there have been few placebo-controlled trials [89].

Semaglutide therapy is associated with mild-to-moderate gastrointestinal adverse events including nausea, vomiting, abdominal discomfort, diarrhoea (up to 60%–80% of patients) and increased risk of gallstones (<5%), though dropout as a result is generally <10%, and their prevalence and severity are attenuated through gradual dose titration to maintenance dose of 2.4 mg once weekly over 16 weeks and/or dose reduction [90, 91]. Weight loss does not appear to be related to the presence of these gastrointestinal side effects [90]. GLP-1RAs have additional benefits of increasing insulin secretion and attenuating glucagon secretion through direct pancreatic actions and improving insulin sensitivity, which directly improves glycaemic control, independent of weight loss [92].

Some initial case reports of non-placebo-controlled treatments suggested that the first- and second-generation GLP-1RAs exenatide and liraglutide may improve glycaemic control, reduce hyperphagia and cause weight loss in some children and adults with PWS [93–102]. However, the formal Phase 2 clinical trial of liraglutide in children/adolescents with PWS sponsored by Novo Nordisk did not affect body mass index significantly, although there was a significant reduction in some questionnaire measures of hyperphagia after 52 weeks of treatment but not after 16 weeks, in adolescents 12–18 years old, but not children 6–12 years old [103].

Semaglutide is more effective than exenatide and liraglutide in reducing weight in children and adults with overweight/obesity without PWS. Case reports in PWS have suggested that semaglutide may be effective in PWS. A 33-year-old man with PWS and T2DM improved weight from 99 to 94 kg over 12 months with semaglutide 1.0 mg once weekly [104]; a 27-year-old man with PWS and T2DM improved weight from 79 to 71 kg over 24 months with semaglutide 0.5 mg once weekly [105]. In a small case series of four adults (two men and two women) with PWS and T2DM, addition of semaglutide 0.5–1.0 mg once weekly reduced

weight in 2/4 patients by 5–10 kg over 12–36 months and reduced haemoglobin A1c (HbA1c) by 0.5%–2% in 3/4 patients [106]. In three adults with PWS without T2DM, a 25-year-old man and a 39-year-old woman (who had previously had gastric bypass surgery) reduced weight by 11% and 14% over 11 and 37 months on semaglutide 1.0 and 2.0 mg weekly, respectively, though a 28-year-old woman only reduced weight by 1% over 37 months on 1.0 mg weekly [107]. Although hyperphagia was not assessed formally in these case reports, appetite was reported as being suppressed in the latter study [107].

A recent paper has reported on the safety and efficacy of semaglutide treatment in an observational cohort of 12 adults with PWS (mean $\pm$ SD age 28.3 ± 10.1 years, 83% female, BMI 46.6 ± 8.2 kg/m², 75% T2DM), treated over a median of 17.2 months [108]. Although semaglutide did not cause weight loss, weight gain prior to treatment stabilized [108]. There were significant decreases in hyperphagia scores on semaglutide treatment without any significant change in the control of the food environment [108]. HbA1c improved in those with elevated baseline levels. There was ≥ 1 side effect in 42% patients, including diarrhoea (though none with nausea, vomiting or exacerbation of constipation), which sometimes prevented or delayed semaglutide dose escalation, but not discontinuation [108].

However, all these cases were open label, observational reports, not all included patients treated up to 2.4 mg once weekly semaglutide dose, and the majority had T2DM. There is also potential benefit in using even higher doses up to 7.2 mg once weekly in the non-PWS population, though with greater risk of side effects [109, 110]. In individuals with obesity but without PWS, there is greater weight loss with semaglutide in those with overweight/obesity without than with T2DM, and so outcomes in more patients with PWS without T2DM are awaited with interest [111]. Although semaglutide is effective for weight loss in adolescents with overweight/obesity without PWS [93], there have been no published case reports of its use in adolescents (or children) with PWS.

Furthermore, there are no published case reports or series to date with the combined GLP-1RA/gastric inhibitory polypeptide analogue tirzepatide, which is more effective for weight loss in those without PWS than

semaglutide [112, 113], though an open-label trial is ongoing in the United States (<https://clinicaltrials.gov/study/NCT06901245>). There have been no completed or known planned placebo-controlled studies of semaglutide or tirzepatide for weight loss and hyperphagia in adults with PWS to date.

Delayed gastric emptying is a commonly reported feature in children and adults with PWS [114, 115], with case reports of severe gastric dilatation and rupture in PWS, including children as young as 5 years, which can be life-threatening [22, 90, 115–119]. In a survey of 154 patients with PWS who had died, 3% were due to gastric rupture related to overeating [115]. In a large PWS cohort in the United States of individuals who died during 1973–2015, gastrointestinal-related problems such as perforation, distension, or obstruction were the causes of death in 10%, with equal distribution over the ages [119].

In children and adults with PWS, there is usually a reduced ability to vomit [120], probably contributed to by diaphragmatic, abdominal and intercostal muscle hypotonia. Choking may occur in PWS and has been reported as a cause of death in 8% of older children and adults [116]. Predisposing factors for choking include hyperphagia, weakness of pharyngeal muscles, gastro-oesophageal reflux and thick saliva. Dysphagia with food residue in pharynx and oesophageal stasis was seen in almost all PWS subjects aged 5–35 years using videofluoroscopy of swallowing [121].

GLP-1RAs can delay gastric emptying and cause gastroparesis [121–130]. Thus, there are concerns that GLP-1RAs might exacerbate or produce gastroparesis in PWS [131] and increase the risk of gastric necrosis or rupture or aspiration. The symptoms of gastroparesis might be masked in PWS by their high pain threshold and reduced vomiting. Although the previous Novo Nordisk clinical trial of liraglutide in PWS did not result in any serious adverse events related to gastrointestinal issues, no formal gastric emptying assessments were performed [98]. Careful observation of side-effect profiles of semaglutide and tirzepatide in PWS will therefore be necessary.

Constipation is known to occur more frequently in children with obesity than without. There are no data in children with PWS, but 20%–40% of adults with PWS are reported to have constipation [132,

133]. In a small cohort of 21 adults with PWS (aged 17–47 years), 40% fulfilled criteria for constipation, and the majority had a faecal mass in the rectum (compared to 12% in patients without PWS) and delayed gastrointestinal transit time [134]. GLP-1RAs can exacerbate constipation as well as cause diarrhoea [90, 91, 135]. Therefore, careful monitoring is essential in PWS, including offering appropriate dietary advice, maintenance of good fluid intake and consideration of probiotics [136–138].

In summary, current studies and reports suggest GLP-1RA is a promising medication for managing metabolic symptoms in PWS, but the effects on body weight and body composition have been mixed. GLP-1 RAs are in general well-tolerated, but careful monitoring is required due to a potential risk for severe adverse effects.

Diazoxide-choline extended release (DCCR) treatment in PWS

Diazoxide-choline extended release (DCCR) is a long-acting crystalline salt formulation of diazoxide. Diazoxide is a potent activator of the ATP-sensitive potassium (K_{ATP}) channel that crosses the blood-brain barrier [139]. Activation of the K_{ATP} channel in NPY/AgRP neurons has the potential to reduce secretion of NPY and AgRP, potent endogenous appetite stimulatory neuropeptides, thereby contributing to a reduction in hyperphagia [139]. These actions are complemented by activation of the K_{ATP} channel in the dorsal motor nucleus of the vagus nerve, pancreatic β -cells and adipocytes to reduce hyperinsulinemia and excess body fat, and to directly or indirectly improve insulin and leptin resistance and satiety [139, 140].

The initial Phase 3 clinical trial data for DCCR were from a 13-week double-anonymized, randomized, placebo-controlled study, which included 127 participants aged 4 years and older who had hyperphagia based on a Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score of $\geq 13/36$ [141]. Unfortunately, this trial was interrupted by the COVID-19 lockdown in March 2020, which changed routines and behaviours for participants, which may have impacted the primary outcome.

A clinically significant improvement in HQ-CT score is considered a decline of >7 points on the questionnaire (out of a maximum score of 36). Although the HQ-CT score in this initial trial did not differ significantly between placebo

and DCCR groups, DCCR had significant positive effects on multiple secondary endpoints, including body composition and Clinical Global Impression of Improvement (CGI-I) [142]. Analysis of results prior to the COVID-19 lockdown showed improvement in HQ-CT score ($p = 0.037$) with DCCR versus placebo, as well as improvement in all secondary endpoints (CGI-I, $p = 0.015$; Caregiver Global Impression of Change, $p = 0.031$; fat mass, $p = 0.003$). Although the primary outcome measure was not statistically significant for the overall group of patients treated with DCCR versus placebo, there was a significant difference between the groups in a sub-analysis of participants with more severe baseline hyperphagia (HQ-CT score $>22/36$ at entry into the trial) [142]. Serum leptin, AG and insulin concentrations were all significantly reduced in the DCCR-treated patients versus placebo, and serum adiponectin was significantly increased in treated patients [142]. These changes in laboratory results suggest that DCCR treatment improves metabolic health in patients with PWS.

The initial clinical trial was followed by an open-label extension (OLE), which included 125 participants who had completed the initial clinical trial. The OLE study demonstrated a continuing decline in HQ-CT score until at least 39 weeks after starting DCCR before plateauing, with a mean decrease of 9 points in HQ-CT score [143]. Additionally, there were sustained significant improvements in all domains of the Prader-Willi Syndrome Profile questionnaire (PWSP), including aggressive behaviours, anxiety, compulsivity, depression, disordered thinking and rigidity/irritability noted in the OLE study [143]. These changes during the trial resulted in a reduction in disease severity as assessed by both clinicians and caregivers. The proportion of participants whose disease severity was rated moderate or worse dropped nearly 50% over 52 weeks, from 88% at baseline to 44.3%.

The open-label portion of the trial was compared to a contemporaneous natural history study in PWS (PATH for PWS) to evaluate effects of DCCR as compared to the clinical natural history of the syndrome [144]. Relative to the PATH for PWS it natural history study cohort, the DCCR-treated cohort showed significant improvements in HQ-CT score over 52 weeks ($p < 0.001$). The DCCR-treated patients also had statistically significant improvements in all domains of the PWSP compared to

those enrolled in PATH for PWS (all $p \leq 0.003$), indicating that DCCR offers meaningful benefits in both hyperphagia and behavioural manifestations for individuals with PWS [144].

As the initial clinical trial failed to meet statistical significance for the primary endpoint, the open-label trial included a 16-week double-blind placebo-controlled randomized withdrawal period. Seventy-seven participants were randomized (DCCR 38; placebo 39) to either remain on DCCR or be withdrawn to placebo for 4 months. A clinically meaningful worsening in HQ-CT score was defined as an increase of 5 points from baseline. The mean increase in HQ-CT total score from baseline to 16 weeks in the placebo arm was 7.6 points from a baseline score of 8.1, representing a 93.8% increase from the score at the start of the randomized withdrawal period ($p = 0.0022$) [145]. The results show that placebo-treated subjects increased the amount of time they asked or talked about food, stole or bargained for food more frequently, were more persistent in asking for food and became more upset when denied food or stopped from asking about food, and food-related behaviours interfered more with their daily lives than those on DCCR [144]. Of note, the effect of DCCR withdrawal was gradual and became significant only at 12 weeks. The effect of withdrawal on HQ-CT total score appeared to be progressive and had not plateaued at 16 weeks. These observations are consistent with results from the prior OLE period [143]. These results also suggest that there is no need to taper DCCR when it is discontinued, as the efficacy of the drug waned gradually over time.

The side effect profile for DCCR is well-established, both from the clinical trials of this medication, and also from its parent molecule, diazoxide (which has been FDA-approved since the 1970s). The most common adverse events from DCCR were as expected based on experience with diazoxide, including hypertrichosis, hyperglycaemia, diabetes and oedema. For participants experiencing a treatment-emergent adverse event (TEAE), 93% experienced a Grades 1 or 2 event [142, 143, 145]. Hypertrichosis was the most common TEAE associated with DCCR treatment across the entirety of the trial ($p < 0.05$). Additionally, DCCR treatment was associated with peripheral oedema (20.2% vs. 9.5%; $p > 0.05$) and hyperglycaemia ($p < 0.05$). These TEAEs rarely resulted

in discontinuation of DCCR (7.2% discontinuation rate across all studies from 2018 to 2025) but occasionally required lowering the dose of DCCR or use of anti-hyperglycaemic agents for diabetes/hyperglycaemia or short-term use of diuretics for oedema. There was only one drug-related serious adverse event that occurred during the trial period (peripheral and pulmonary oedema in the setting of an unrelated concurrent pneumonia) [142]. All of the adverse events noted during the trial were not unexpected based on clinical experience with diazoxide and the natural history of PWS.

This was the first time a medication had been shown to safely and sustainably improve hyperphagia in individuals with PWS. The unexpected benefit of the trial being interrupted by COVID-19 was that investigators were able to observe the effects and side effects of DCCR over time. The results of this long-term trial resulted in FDA-approval of the drug in the United States in March 2025, marking the first FDA-approved therapy for hyperphagia in PWS.

Discussion

Our review has shown that early intervention with strict and controlled dietary routines, using psychological food security calorie restriction, and controlled food access (locked pantries/refrigerators) remains essential, along with scheduled weighing and support to the person with PWS and caregivers. Furthermore, physical activity should be implemented early and proceed throughout childhood and adulthood, and hormone deficiencies replaced. Early OT treatment in infants with PWS has shown long-term positive effects, with a less severe disorder at 3 and 4 years but it has yet to be licensed for PWS, treatment with GLP-1 RA has had mixed effects and is being further explored, whereas treatment with DCCR is the first approved treatment for hyperphagia in PWS, showing significant effects on severe hyperphagia and obesity.

Other potential treatments

Treatment for hyperphagia and obesity in PWS is shifting from being purely calorie restriction and behavioural management to targeted pharmacological and non-pharmacological therapies.

Pharmacological treatments

In addition to the drugs described in this review, several drugs have been developed or are being developed for treatment of hyperphagia and obesity in PWS.

Setmelanotide, a melanocortin-4 receptor (MC4R) agonist, exerts its effects in the hypothalamus, resulting in increased satiety and reduced hunger. Setmelanotide is approved for long-term weight management in patients with obesity due to POMC, PCSK1, LEPR deficiency or Bardet-Biedl syndrome [146]. Preliminary results from Phase 2 studies of setmelanotide in PWS demonstrated reduced BMI and hyperphagia (NCT02311673 and NCT06772597) and a Phase 1 study of a weekly MC4R agonist, without causing the hyperpigmentation that can occur with setmelanotide, is ongoing (NCT06239116). The FDA has in March 2026 approved an expanded indication for setmelanotide to treat children and adults with acquired structural hypothalamic obesity.

ARD-101 is an oral, G-protein-coupled receptor agonist that activates bitter taste receptors (TAS2R) in the gut, stimulating the release of satiety hormones such as CCK and GLP-1. Phase 2 trials in PWS (NCT05153434) have shown reduced hyperphagia and improvement in related behaviour. ARD-101 was well-tolerated in the Phase 3, randomized, double-anonymized, placebo-controlled study (NCT06828861), but the OLE study (NCT07197034) was recently paused due to cardiac side effects.

Livuletide (AZP-531) is a peptide analogue of unacylated ghrelin (UAG). In PWS, circulating concentrations of the orexigenic hormone AG are high, whereas those of UAG, which may counteract many of AG's effects, are low [147]. Low plasma UAG concentrations result in an increased AG/UAG ratio, which has been associated with the development of hyperphagia [148]. Phase 2b/3 randomized, placebo-controlled trials (NCT03790865) indicated that AZP-531 was well-tolerated and effective at reducing appetite scores and improving metabolic parameters, particularly in patients with higher baseline hyperphagia [149]. No serious adverse events were reported, but the primary endpoint was not met, and the trial was discontinued.

The cannabinoid-1 receptor (CB1R) is most abundantly expressed in the hypothalamus and other brain regions associated with appetite regulation and food reward and plays an important role in regulating eating behaviour [150]. The first-in-class CB1R antagonist, rimonabant, was an effective treatment for obesity [151]. However, it had serious neuropsychiatric side effects and was withdrawn from the market in 2008. A peripherally acting CB1R antagonist, JD5037, was developed, and an early clinical trial in PWS showed reduced body weight, reversed hyperphagia and improved metabolic parameters without the neuropsychiatric side effects of the older agent [152]. However, further trials were discontinued due to unforeseen complications [153].

Beloranib inhibits methionine aminopeptidase 2 (MetAP2), which prevents removal of the proximal (amino terminus) methionine residue from proteins cleaved by MetAP2 [154]. Beloranib reduced food intake, body weight and body fat, and a Phase 3 study in PWS (NCT02179151) demonstrated significant and clinically meaningful improvements in hyperphagia-related behaviours and weight loss [155], but further development was discontinued after deaths from pulmonary embolism.

Non-pharmacological treatments

Recent developments in advanced neuroimaging have led to an increasing understanding of PWS as a neural circuit disorder and subsequent interest in neuromodulatory therapies. Several non-invasive and invasive neuromodulation methods—including vagus nerve stimulation (VNS), transcranial direct current stimulation, repetitive transcranial magnetic stimulation and deep brain stimulation—have all been reported to be potentially promising treatments in PWS. A recently published systematic literature review of a total of 47 patients with PWS who had undergone neuromodulation therapy reported that a potential for treating PWS by targeting brain circuits related to hyperphagia, behavioural issues and appetite control was observed for some of the methods [156]. The studies are in early phases, focusing on safety, feasibility and identifying the optimal neural targets to manage the symptoms of PWS.

Bariatric surgery (e.g., sleeve gastrectomy and gastric bypass) in PWS is considered a high-risk, adjunctive treatment for severe, uncontrollable obesity rather than a cure. Data from patients

reported in the literature suggest that bariatric surgery can lead to significant short-term weight loss and ameliorate comorbidities in carefully selected individuals [157]. However, the persistent hyperphagia in PWS incurs a high risk of weight regain over time, severely reducing long-term efficacy. In addition, the risk of life-threatening complications, such as acute gastric dilation leading to gastric rupture or necrosis, anastomotic leaks and sepsis, severe gastrointestinal bleeding and venous thromboembolism, is high [158]. In addition, intra-abdominal life-threatening conditions are difficult to diagnose because of aberrant pain awareness and reporting in patients with PWS. Therefore, bariatric surgery is not currently recommended for people with PWS [158].

Cognitive behavioural therapy has a limited role in managing hyperphagia in PWS and is not a primary treatment, although it may be a supportive adjunct within multidisciplinary care [159].

Conclusion

An effective and safe treatment is necessary for managing both hyperphagia and obesity in patients with PWS to avoid development of morbid obesity over time. Psychological food security manages both calorie restriction and behaviour by establishing predictability and expectations for food in the reward network of the brain. Controlled food access and scheduled physical activity remain crucial interventions. OT treatment of infants with PWS results in better metabolic outcomes, whereas studies of GLP-1RA have shown mixed effects on weight and hyperphagia, and further studies are ongoing. DCCR is the first approved treatment of hyperphagia in PWS, and promising results, particularly in managing severe hyperphagia, reducing fat mass and improving behavioural issues, have been reported. Several other drugs and therapies have been explored or are currently undergoing clinical trials to address these issues. Although some trials have been discontinued due to adverse events or not meeting endpoints, progress is being made in pharmacological therapies to control hyperphagia and reduce weight. DCCR is only approved in the United States, and patients in other countries still face unmet medical needs. More studies and long-term studies are needed before all issues with management of hyperphagia and obesity in PWS have been answered.

In our opinion, future progress in treating hyperphagia and obesity in PWS will probably depend on a shift from symptomatic management towards biologically targeted and mechanism-driven interventions. Hyperphagia in PWS arises from defects in the appetite/satiety signalling and neural circuit regulation, and long-term advances will require interventions addressing the underlying neurogenic mechanisms, including the hypothalamus and dopamine system. Emerging strategies such as epigenetic reactivation of silenced paternal genes within the 15q11.2–13 locus, alongside increasingly precise early neuromodulation approaches, offer the potential for disease-modifying effects. In parallel, there is a critical need to develop and validate objective biomarkers of hyperphagia and treatment response, enabling stratified and genotype-informed care. Importantly, future therapeutic frameworks should view pharmacological, behavioural and environmental interventions as complementary parts of integrated care. Such an approach, combining early-life intervention, precision pharmacotherapy and adaptive environmental design, holds the greatest promise for altering the natural history of PWS and substantially reducing the lifelong burden of hyperphagia and obesity.

Author contributions

Charlotte Höybye: Conceptualization; writing—original draft; writing—review and editing. **Janice Foster:** Writing—original draft; writing—review and editing. **Anthony P. Goldstone:** Writing—original draft; writing—review and editing. **Linda Gourash:** Writing—original draft; writing—review and editing. **Jennifer Miller:** Writing—original draft; writing—review and editing. **Maithé Tauber:** Writing—original draft; writing—review and editing.

Conflict of interest statement

Charlotte Höybye is Principal Investigator for a clinical trial for Harmony Biosciences (PWS) and Debiopharm (acromegaly) and has received speaker honorarium fee from Soleno Therapeutics. Janice Foster has received a speaker honorarium fee from Soleno Therapeutics. Anthony P. Goldstone is a consultant for Rhythm Pharmaceuticals and Novo Nordisk; has been a clinical investigator for clinical trials sponsored by Rhythm Pharmaceuticals, Millendo Therapeutics and Soleno Therapeutics; has been a consultant for Eli Lilly, Evidera, Helsinn Healthcare S.A, Idera

Pharmaceuticals, Radius Health, Soleno Therapeutics, Tonix Pharmaceuticals and Vida Ventures; has been on Advisory Boards for Radius Health and Millendo Therapeutics; has been on Data Safety Monitoring Committee for Novo Nordisk and has received speaker fees from Eli Lilly, Novo Nordisk, Soleno Therapeutics and Rhythm Pharmaceuticals, and research support from Novo Nordisk. Linda Gourash has received a consultant fee from Soleno Therapeutics. Jennifer Miller has received research grants from Soleno Therapeutics, Rhythm Therapeutics, Harmony Biosciences and Aardvark Therapeutics. Maithé Tauber has been a member of medical advisory board and a Chief Investigator on clinical trials for Millendo Therapeutics and Novo Nordisk; Principal Investigator for clinical trials on OT treatment in PWS, Head of the scientific advisory board of OT4B, and has three patents for OT in PWS.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current review.

References

- 1 Bar C, Diene G, Molinas C, Bieth E, Casper C, Tauber M, et al. Early diagnosis and care is achieved but should be improved in infants with Prader-Willi syndrome. *Orphanet J Rare Dis*. 2017;**12**:118. <https://doi.org/10.1186/s13023-017-0673-6>.
- 2 Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi syndrome. In: Adam MP, Bick S, Mirzaa GM, Wallace SE, Amemiya A, editors. *GeneReviews*® [Internet]. Seattle, WA: University of Washington; 1993–2026. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1330/>.
- 3 Correa-da-Silva F, Fliers E, Swaab DF, Yi C-X. Hypothalamic neuropeptides and neurocircuitries in Prader-Willi syndrome. *J Neuroendocrinol*. 2021;**33**:e12994. <https://doi.org/10.1111/jne.12994>.
- 4 Tauber M, Höybye C. Endocrine disorders in Prader-Willi syndrome: a model to understand and treat hypothalamic dysfunction. *Lancet Diabetes Endocrinol*. 2021;**9**:235–46. [https://doi.org/10.1016/S2213-8587\(21\)00002-4](https://doi.org/10.1016/S2213-8587(21)00002-4).
- 5 Roof E, Stone W, MacLean W, Feurer ID, Thompson T, Butler MG. Intellectual characteristics of Prader-Willi syndrome: comparison of genetic subtypes. *J Intellect Disabil Res*. 2000;**44**(Pt 1):25–30. <https://doi.org/10.1046/j.1365-2788.2000.00250.x>.
- 6 Crinò A, Schiaffini R, Ciampalini P, Spera S, Beccaria L, Benzi F, et al. Hypogonadism and pubertal development in Prader-Willi syndrome. *Eur J Pediatr*. 2003;**162**:327–33. <https://doi.org/10.1007/s00431-002-1132-4>.
- 7 Gantz MG, Andrews SM, Wheeler AC. Food and non-food-related behavior across settings in children with Prader-Willi syndrome. *Genes (Basel)*. 2020;**11**:204. <https://doi.org/10.3390/genes11020204>.

- 8 Kayadjanian N, Schwartz L, Farrar E, Comtois KA, Strong TV. High levels of caregiver burden in Prader-Willi syndrome. *PLoS ONE*. 2018;**13**:e0194655. <https://doi.org/10.1371/journal.pone.0194655>.
- 9 Heymsfield SB, Avena NM, Baier L, Brantley P, Bray GA, Burnett LC, et al. Hyperphagia: current concepts and future directions. *Obesity (Silver Spring)*. 2014;**22**(Suppl 1):S1–S17. <https://doi.org/10.1002/oby.20646>.
- 10 Høybye C, Petersson M. The role of the arcuate nucleus in regulating hunger and satiety in Prader-Willi syndrome. *Curr Issues Mol Biol*. 2025;**47**:192. <https://doi.org/10.3390/cimb47030192>.
- 11 Brown SSG, Manning KE, Fletcher P, Holland A. In vivo neuroimaging evidence of hypothalamic alteration in Prader-Willi syndrome. *Brain Commun*. 2022;**4**(5):fcac229. <https://doi.org/10.1093/braincomms/fcac229>.
- 12 DelParigi A, Tschöp M, Heiman ML, Salbe AD, Vozarova B, Sell SM, et al. High circulating ghrelin: a potential cause for hyperphagia and obesity in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2002;**87**:5461–64. <https://doi.org/10.1210/jc.2002-020871>.
- 13 Damen L, Donze SH, Kuppens RJ, Bakker NE, de Graaff LCG, van der Velden JAEM, et al. Three years of growth hormone treatment in young adults with Prader-Willi syndrome: sustained positive effects on body composition. *Orphanet J Rare Dis*. 2020;**15**:163. <https://doi.org/10.1186/s13023-020-01440-6>.
- 14 Tan Q, Orsso CE, Deehan EC, Triador L, Field CJ, Tun HM, et al. Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: a narrative review. *Obes Rev*. 2020;**21**:e12992. <https://doi.org/10.1111/obr.12992>.
- 15 Goldstone AP, Thomas EL, Brynes AE, Bell JD, Frost G, Saeed N, et al. Visceral adipose tissue and metabolic complications of obesity are reduced in Prader-Willi syndrome female adults: evidence for novel influences on body fat distribution. *J Clin Endocrinol Metab*. 2001;**86**:4330–38. <https://doi.org/10.1210/jcem.86.9.7814>.
- 16 Alsaif M, Elliot SA, MacKenzie ML, Prado CM, Field CJ, Haqq AM, et al. Energy metabolism profile in individuals with Prader-Willi syndrome and implications for clinical management: a systematic review. *Adv Nutr*. 2017;**8**:905–15. <https://doi.org/10.3945/an.117.016253>.
- 17 Morales JS, Valenzuela PL, Pareja-Galeano H, Rincón-Castaneda C, Rubin DA, Lucia A, et al. Physical exercise and Prader-Willi syndrome: a systematic review. *Clin Endocrinol (Oxf)*. 2019;**90**:649–61. <https://doi.org/10.1111/cen.13953>.
- 18 Bellicha A, Coupaye M, Mosbah H, Tauber M, Oppert J-M, Poitou C, et al. Physical activity in patients with Prader-Willi syndrome: a systematic review of observational and interventional studies. *J Clin Med*. 2021;**10**:2528. <https://doi.org/10.3390/jcm10112528>.
- 19 Miller JL, Tan M. Dietary management for adolescents with Prader-Willi syndrome. *Adolesc Health Med Ther*. 2020;**11**:113–18. <https://doi.org/10.2147/AHMT.S214893>.
- 20 Crinò A, Fintini D, Bocchini S, Grugni G. Obesity management in Prader-Willi syndrome: current perspectives. *Diabetes Metab Syndr Obes*. 2018;**11**:579–93. <https://doi.org/10.2147/DMSO.S141352>.
- 21 Bellis SA, Kuhn I, Adams S, Mullarkey L, Holland A. The consequences of hyperphagia in people with Prader-Willi syndrome: a systematic review of studies of morbidity and mortality. *Eur J Med Genet*. 2022;**65**:104379. <https://doi.org/10.1016/j.ejmg.2021.104379>.
- 22 Giesecke J, Oskarsson A, Petersson M, Nordenvall AS, Tettamanti G, Nordgren A, et al. Comorbidities, endocrine medications, and mortality in Prader-Willi syndrome: a Swedish register study. *J Clin Med*. 2025;**14**:1307. <https://doi.org/10.3390/jcm14041307>.
- 23 Rahman QFA, Jufri NF, Hamid A. Hyperphagia in Prader-Willi syndrome with obesity: from development to pharmacological treatment. *Intractable Rare Dis Res*. 2023;**12**:5–12. <https://doi.org/10.5582/irdr.2022.01127>.
- 24 Mahmoud R, Kimonis V, Butler MG. Clinical trials in Prader-Willi syndrome: a review. *Int J Mol Sci*. 2023;**24**:2150. <https://doi.org/10.3390/ijms24032150>.
- 25 Whitman BY. Prader-Willi syndrome: the more we know, the less we know. *Missouri Med*. 2024;**121**:235.
- 26 Miller JL, Lynn CH, Driscoll DC, Goldstone AP, Gold J-A, Kimonis V, et al. Nutritional phases in Prader-Willi syndrome. *Am J Med Genet A*. 2011;**155A**:1040–49. <https://doi.org/10.1002/ajmg.a.33951>.
- 27 Bravo JP, Pérez PD, Canals Cifuentes A. Nutritional phases of Prader-Willi syndrome. *Andes Pediatr*. 2021;**92**:359–66. <https://doi.org/10.32641/andespediatr.v92i3.2400>.
- 28 Johnson LM. A genetic condition that spans both extremes of the nutritional spectrum. *Pract Lab Med*. 2024;**40**:e00405. <https://doi.org/10.1016/j.plabm.2024.e00405>.
- 29 Kweh FA, Sulsona CR, Miller JL, Driscoll DJ. Hyperinsulinemia is a probable trigger for weight gain and hyperphagia in individuals with Prader-Willi syndrome. *Obes Sci Pract*. 2023;**9**:383–94. <https://doi.org/10.1002/osp4.663>.
- 30 Kweh FA, Miller JL, Sulsona CR, Wasserfall C, Atkinson M, Shuster JJ, et al. Hyperghrelinemia in Prader-Willi syndrome begins in early infancy long before the onset of hyperphagia. *Am J Med Genet A*. 2015;**167A**:69–79. <https://doi.org/10.1002/ajmg.a.36810>.
- 31 Grootjen LN, Diene G, Molinas C, Beauloye V, Huisman TM, Visser JA, et al. Longitudinal changes in acylated versus unacylated ghrelin levels may be involved in the underlying mechanisms of the switch in nutritional phases in Prader-Willi syndrome. *Horm Res Paediatr*. 2024;**97**:343–52. <https://doi.org/10.1159/000534560>.
- 32 Tauber M, Coupaye M, Diene G, Molinas C, Valette M, Beauloye V. Prader-Willi syndrome: a model for understanding the ghrelin system. *J Neuroendocrinol*. 2019;**31**(7):e12728. <https://doi.org/10.1111/jne.12728>.
- 33 Miller JL, Lacroix A, Bird LM, Shoemaker AH, Haqq A, Deal CL, et al. The efficacy, safety, and pharmacology of a ghrelin O-acyltransferase inhibitor for the treatment of Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2022;**107**(6):e2373–80. <https://doi.org/10.1210/clinem/dgac105>.
- 34 Currie G, Estefan A, Caine V. “Unable to feed my hungry child”: experiences of mothers caring for children with Prader-Willi syndrome. *Glob Qual Nurs Res*. 2024;**11**:23333936241242929. <https://doi.org/10.1177/23333936241242929>.
- 35 Zipf WB, Berntson GG. Characteristics of abnormal food-intake patterns in children with Prader-Willi syndrome and

- study of effects of naloxone. *Am J Clin Nutr*. 1987;**46**:277–81. <https://doi.org/10.1093/ajcn/46.2.277>.
- 36 Holsen LM, Zarcone JR, Brooks WM, Butler MG, Thompson TI, Ahluwalia JS, et al. Neural mechanisms underlying hyperphagia in Prader-Willi syndrome. *Obesity (Silver Spring)*. 2006;**14**:1028–37. <https://doi.org/10.1038/oby.2006.118>.
 - 37 Holsen LM, Savage CR, Martin LE, Bruce AS, Lepping RJ, Ko E, et al. Importance of reward and prefrontal circuitry in hunger and satiety: Prader-Willi syndrome vs simple obesity. *Int J Obes (Lond)*. 2012;**36**:638–47. <https://doi.org/10.1038/ijo.2011.204>.
 - 38 Åkefeldt A. Water intake and risk of hyponatraemia in Prader-Willi syndrome. *J Intellect Disabil Res*. 2009;**53**:521–28. <https://doi.org/10.1111/j.1365-2788.2009.01169.x>.
 - 39 Coupaye M, Pellikaan K, Goldstone AP, Crinò A, Grunig G, Markovic TP, et al. Hyponatremia in children and adults with Prader-Willi syndrome: a survey involving seven countries. *J Clin Med*. 2021;**10**:3555. <https://doi.org/10.3390/jcm10163555>.
 - 40 Huang Z, Zheng H, Wang L, Ding S, Li R, Qing Y, et al. Aberrant brain structural-functional coupling and structural/functional network topology explain developmental delays in pediatric Prader-Willi syndrome. *Eur Child Adolesc Psychiatry*. 2025;**34**(7):2155–67. <https://doi.org/10.1007/s00787-024-02631-3>.
 - 41 Xu M, Zhang Y, von Deneen KM, Zhu H, Gao JH. Brain structural alterations in obese children with and without Prader-Willi syndrome. *Hum Brain Mapp*. 2017;**38**(8):4228–38. <https://doi.org/10.1002/hbm.23660>.
 - 42 Forster J, Fangman E, Duis J, Manzardo A. Developmental characterization of phenotypic behaviors. Presented at Clinical and scientific meeting of the IPWSO conference, Phoenix, AZ, USA; 2025.
 - 43 Santos M, Uppal N, Butti C, Wicinski B, Schmeidler J, Giannakopoulos P, et al. Von Economo neurons in autism: a stereologic study of the frontoinsula cortex in children. *Brain Res*. 2011;**1380**:206–17. <https://doi.org/10.1016/j.brainres.2010.08.067>.
 - 44 Forster JL, Gourash LM, Royle M. A preliminary description of PWS behaviors across the lifespan: stability and change. Presented at: 30th annual PWSA (USA) national conference, Milwaukee, WI, USA; 2008.
 - 45 Gourash LM, Forster JL, editors. *Food, behavior and beyond: practical management for the child and adult with PWS [DVD]*. Sarasota, FL, USA: IPWSO; PWSA-USA; 2005.
 - 46 Epstein LH. A brief history and future of the traffic light diet. *Curr Dev Nutr*. 2022;**6**:nzac120. <https://doi.org/10.1093/cdn/nzac120>.
 - 47 Balko K. Red yellow green system for weight management. Toronto, Ontario, Canada: Ontario Prader-Willi Syndrome Association; 2005.
 - 48 Berall G, Gourash LM, Forster JL. Lessons from Prader-Willi syndrome: integrating weight and behavior management. Presented at: 52nd annual meeting of the American Academy of Child and Adolescent Psychiatry, Toronto, Canada; 2005.
 - 49 Swaab DF, Purba JS, Hofman MA. Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 1995;**80**:573–79. <https://doi.org/10.1210/jcem.80.2.7852513>.
 - 50 Muscatelli F, Arous DN, Massacrier A, Boccaccio I, Le Moal M, Cau P, et al. Disruption of the mouse Necdin gene results in hypothalamic and behavioral alterations reminiscent of the human Prader-Willi syndrome. *Hum Mol Genet*. 2000;**9**:3101–10. <https://doi.org/10.1093/hmg/9.20.3101>.
 - 51 Schaller F, Watrin F, Sturny R, Massacrier A, Szepietowski P, Muscatelli F. A single postnatal injection of oxytocin rescues the lethal feeding behaviour in mouse newborns deficient for the imprinted Magel2 gene. *Hum Mol Genet*. 2010;**19**:4895–905. <https://doi.org/10.1093/hmg/ddq424>.
 - 52 Meziane H, Schaller F, Bauer S, Villard C, Matarazzo V, Riet F, et al. An early postnatal oxytocin treatment prevents social and learning deficits in adult mice deficient for Magel2, a gene involved in Prader-Willi syndrome and autism. *Biol Psychiatry*. 2015;**78**:85–94. <https://doi.org/10.1016/j.biopsych.2014.11.010>.
 - 53 Aulinas A, Lawson EA. The oxytocin system and implications for oxytocin deficiency in hypothalamic-pituitary disease. *Endocr Rev*. 2025;**46**:518–48. <https://doi.org/10.1210/endrev/bnaf008>.
 - 54 Maejima Y, Yokota S, Nishimori K, Shimomura K. The anorexigenic neural pathways of oxytocin and their clinical implication. *Neuroendocrinology*. 2018;**107**:91–104. <https://doi.org/10.1159/000489263>.
 - 55 Camerino C. Oxytocin's regulation of thermogenesis may be the link to Prader-Willi syndrome. *Curr Issues Mol Biol*. 2023;**45**:4923–35. <https://doi.org/10.3390/cimb45060313>.
 - 56 Tauber M, Mantoulan C, Copet P, Jauregui J, Demeer G, Diene G, et al. Oxytocin may be useful to increase trust in others and decrease disruptive behaviours in patients with Prader-Willi syndrome: a randomised placebo-controlled trial in 24 patients. *Orphanet J Rare Dis*. 2011;**6**:47. <https://doi.org/10.1186/1750-1172-6-47>.
 - 57 Einfeld SL, Smith E, McGregor IS, Steinbeck K, Taffe J, Rice LJ, et al. A double-blind randomized controlled trial of oxytocin nasal spray in Prader-Willi syndrome. *Am J Med Genet A*. 2014;**164A**:2232–39. <https://doi.org/10.1002/ajmg.a.36653>.
 - 58 Kuppens RJ, Donze SH, Hokken-Koelega ACS. Promising effects of oxytocin on social and food-related behaviour in young children with Prader-Willi syndrome: a randomized, double-blind, controlled crossover trial. *Clin Endocrinol (Oxf)*. 2016;**85**:979–87. <https://doi.org/10.1111/cen.13169>.
 - 59 Miller JL, Tamura R, Butler MG, Kimonis V, Sulsona C, Gold J-A, et al. Oxytocin treatment in children with Prader-Willi syndrome: a double-blind, placebo-controlled, crossover study. *Am J Med Genet A*. 2017;**173**:1243–50. <https://doi.org/10.1002/ajmg.a.38160>.
 - 60 Damen L, Grootjen LN, Juriaans AF, Donze SH, Huisman TM, Visser JA, et al. Oxytocin in young children with Prader-Willi syndrome: results of a randomized, double-blind, placebo-controlled, crossover trial investigating 3 months of oxytocin. *Clin Endocrinol (Oxf)*. 2021;**94**:774–85. <https://doi.org/10.1111/cen.14387>.
 - 61 Hollander E, Levine KG, Ferretti CJ, Freeman K, Doernberg E, Desilva N, et al. Intranasal oxytocin versus placebo for hyperphagia and repetitive behaviors in children with Prader-Willi Syndrome: a randomized controlled pilot trial. *J*

- Psychiatr Res.* 2021;**137**:643–51. <https://doi.org/10.1016/j.psychires.2020.11.006>.
- 62 Dykens EM, Miller J, Angulo M, Roof E, Reidy M, Hatoum HT, et al. Intranasal carbetocin reduces hyperphagia in individuals with Prader-Willi syndrome. *JCI Insight.* 2018;**3**:e98393. <https://doi.org/10.1172/jci.insight.98333>.
 - 63 Roof E, Deal CL, McCandless SE, Cowan RL, Miller JL, Hamilton JK, et al. Intranasal carbetocin reduces hyperphagia, anxiousness, and distress in Prader-Willi syndrome: CARE-PWS phase 3 trial. *J Clin Endocrinol Metab.* 2023;**108**:1696–708. <https://doi.org/10.1210/clinem/dgad015>.
 - 64 Shalma NM, Alsharabasy MA, Taha AM, Alsawareah A, Manirambona E, Ahmed SK, et al. The Efficacy of intranasal oxytocin in patients with Prader-Willi syndrome: a systematic review and meta-analysis. *Diabetes Metab Syndr.* 2023;**17**:102711. <https://doi.org/10.1016/j.dsx.2023.102711>.
 - 65 Carter CS, Kenkel WM, MacLean EL, Wilson SR, Perkeybile AM, Yee JR, et al. Is oxytocin “nature’s medicine”? *Pharmacol Rev.* 2020;**72**:829–61. <https://doi.org/10.1124/pr.120.019398>.
 - 66 Feigerlova E, Diene G, Oliver I, Gennaro I, Salles JP, Arnaud C, et al. Elevated insulin-like growth factor-I values in children with Prader-Willi syndrome compared with growth hormone (GH) deficiency children over two years of GH treatment. *J Clin Endocrinol Metab.* 2010;**95**:4600–4608. <https://doi.org/10.1210/jc.2009-1831>.
 - 67 Salles J, Eddiry S, Amri S, Galindo M, Lacassagne E, George S, et al. Differential DNA methylation in iPSC-derived dopaminergic neurons: a step forward on the role of SNORD116 microdeletion in the pathophysiology of addictive behavior in Prader-Willi syndrome. *Mol Psychiatry.* 2024;**29**:2742–52. <https://doi.org/10.1038/s41380-024-02542-4>.
 - 68 Chevalleyre V, Dayanithi G, Moos FC, Desarménien MG. Developmental regulation of a local positive autocontrol of supraoptic neurons. *J Neurosci.* 2000;**20**:5813–19. <https://doi.org/10.1523/JNEUROSCI.20-15-05813.2000>.
 - 69 Rice LJ, Agu J, Carter CS, Harris JC, Nazaroo HP, Naanai H, et al. The relationship between endogenous oxytocin and vasopressin levels and the Prader-Willi syndrome behaviour phenotype. *Front Endocrinol (Lausanne).* 2023;**14**:1183525. <https://doi.org/10.3389/fendo.2023.1183525>.
 - 70 Valette M, Diene G, Glattard M, Cortadellas J, Molinas C, Faye S, et al. Early oxytocin treatment in infants with Prader-Willi syndrome is safe and is associated with better endocrine, metabolic and behavioral outcomes. *Orphanet J Rare Dis.* 2025;**20**:96. <https://doi.org/10.1186/s13023-025-03560-3>.
 - 71 Tauber M, Diene G, Fichaux-Bourin P, Pinto G, Gueorguieva I, Nicolino M, et al. Oxytocin in infants with Prader-Willi syndrome to improve dysphagia and disease trajectory. *Orphanet J Rare Dis.* 2026;**21**:88. <https://doi.org/10.1186/s13023-026-04214-8>.
 - 72 Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet.* 2021;**397**:971–84. [https://doi.org/10.1016/S0140-6736\(21\)00213-0](https://doi.org/10.1016/S0140-6736(21)00213-0).
 - 73 Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. *JAMA.* 2021;**325**:1414–25. <https://doi.org/10.1001/jama.2021.3224>.
 - 74 Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA.* 2021;**325**:1403–13. <https://doi.org/10.1001/jama.2021.1831>.
 - 75 Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med.* 2021;**384**:989–1002. <https://doi.org/10.1056/NEJMoa2032183>.
 - 76 Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med.* 2022;**28**:2083–91. <https://doi.org/10.1038/s41591-022-02026-4>.
 - 77 Kadowaki T, Isendahl J, Khalid U, Lee SY, Nishida T, Ogawa W, et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an East Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. *Lancet Diabetes Endocrinol.* 2022;**10**:193–206. [https://doi.org/10.1016/S2213-8587\(22\)00008-0](https://doi.org/10.1016/S2213-8587(22)00008-0).
 - 78 Rubino DM, Greenway FL, Khalid U, O’Neil PM, Rosenstock J, Sørrig R, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA.* 2022;**327**:138–50. <https://doi.org/10.1001/jama.2021.23619>.
 - 79 Weghuber D, Barrett T, Barrientos-Pérez M, Gies I, Hesse D, Jeppesen OK, et al. Once-weekly semaglutide in adolescents with obesity. *N Engl J Med.* 2022;**387**:2245–57. <https://doi.org/10.1056/NEJMoa2208601>.
 - 80 Gibbons C, Blundell J, Tetens Hoff S, Dahl K, Bauer R, Bækdal T, et al. Effects of oral semaglutide on energy intake, food preference, appetite, control of eating and body weight in subjects with type 2 diabetes. *Diabetes Obes Metab.* 2021;**23**:581–88. <https://doi.org/10.1111/dom.14255>.
 - 81 Wharton S, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, et al. Two-year effect of semaglutide 2.4 mg on control of eating in adults with overweight/obesity: STEP 5. *Obesity (Silver Spring).* 2023;**31**:703–15. <https://doi.org/10.1002/oby.23673>.
 - 82 Kolotkin RL, Jeppesen OK, Baker-Knight J, Lee SY, Tokita A, Kadowaki T, et al. Effect of once-weekly subcutaneous semaglutide 2.4 mg on weight- and health-related quality of life in an East Asian population: patient-reported outcomes from the STEP 6 trial. *Clin Obes.* 2023;**13**:e12589. <https://doi.org/10.1111/cob.12589>.
 - 83 Rubino D, Bjorner JB, Rathor N, Sharma AM, von Huth Smith L, Wharton S, et al. Effect of semaglutide 2.4 mg on physical functioning and weight- and health-related quality of life in adults with overweight or obesity: patient-reported outcomes from the STEP 1–4 trials. *Diabetes Obes Metab.* 2024;**26**:2945–55. <https://doi.org/10.1111/dom.16205>.
 - 84 Robert SA, Rohana AG, Shah SA, Chinnna K, Wan Mohamud WN, Kamaruddin NA, et al. Improvement in binge eat-

- ing in non-diabetic obese individuals after 3 months of treatment with liraglutide: a pilot study. *Obes Res Clin Pract.* 2015;**9**:301–4. <https://doi.org/10.1016/j.orcp.2015.03.005>.
- 85 Chao AM, Wadden TA, Walsh OA, Gruber KA, Alamuddin N, Berkowitz RI, et al. Effects of liraglutide and behavioral weight loss on food cravings, eating behaviors, and eating disorder psychopathology. *Obesity (Silver Spring)*. 2019;**27**:2005–10. <https://doi.org/10.1002/oby.22653>.
 - 86 Da Porto A, Casarsa V, Colussi G, Casarsa V, Colussi G, Catena C, et al. Dulaglutide reduces binge episodes in type 2 diabetic patients with binge eating disorder: a pilot study. *Diabetes Metab Syndr.* 2020;**14**:289–92. <https://doi.org/10.1016/j.dsx.2020.03.009>.
 - 87 Richards J, Bang N, Ratliff EL, Paszkowiak MA, Khorgami Z, Khalsa SS, et al. Successful treatment of binge eating disorder with the GLP-1 agonist semaglutide: a retrospective cohort study. *Obes Pillars.* 2023;**7**:100080. <https://doi.org/10.1016/j.obpill.2023.100080>.
 - 88 Aoun L, Almaridini S, Saliba F, Haddadin F, Mourad O, Jdaidani J, et al. GLP-1 receptor agonists: a novel pharmacotherapy for binge eating (binge eating disorder and bulimia nervosa)? A systematic review. *J Clin Transl Endocrinol.* 2024;**35**:100333. <https://doi.org/10.1016/j.jcte.2024.100333>.
 - 89 Allison KC, Chao AM, Bruzas MB, McCuen-Wurst C, Jones E, McAllister C, et al. A pilot randomized controlled trial of liraglutide 3.0 mg for binge eating disorder. *Obes Sci Pract.* 2023;**9**:127–36. <https://doi.org/10.1002/osp4.619>.
 - 90 Wharton S, Calanna S, Davies M, Dicker D, Goldman B, Lingvay I, et al. Gastrointestinal tolerability of once-weekly semaglutide 2.4 mg in adults with overweight or obesity, and the relationship between gastrointestinal adverse events and weight loss. *Diabetes Obes Metab.* 2022;**24**:94–105. <https://doi.org/10.1111/dom.14551>.
 - 91 Ismaiel A, Scarlata GGM, Boitos I, Leucuta DC, Popa SL, Al Srouji N, et al. Gastrointestinal adverse events associated with GLP-1 RA in non-diabetic patients with overweight or obesity: a systematic review and network meta-analysis. *Int J Obes (Lond)*. 2025;**49**:1946–57. <https://doi.org/10.1038/s41366-025-01859-6>.
 - 92 Liu QK. Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. *Front Endocrinol (Lausanne)*. 2024;**15**:1431292. <https://doi.org/10.3389/fendo.2024.1431292>.
 - 93 Cyganek K, Koblik T, Kozek E, Koblik T, Kozek E, Wojcik M, et al. Liraglutide therapy in Prader-Willi syndrome. *Diabet Med.* 2011;**28**:755–56. <https://doi.org/10.1111/j.1464-5491.2011.03280.x>.
 - 94 Seetho IW, Jones G, Thomson GA, Fernando DJ. Treating diabetes mellitus in Prader-Willi syndrome with exenatide. *Diabetes Res Clin Pract.* 2011;**92**:e1–e2. <https://doi.org/10.1016/j.diabres.2010.12.009>.
 - 95 Sze L, Purtell L, Jenkins A, Loughnan G, Smith E, Herzog H, et al. Effects of a single dose of exenatide on appetite, gut hormones, and glucose homeostasis in adults with Prader-Willi syndrome. *J Clin Endocrinol Metab.* 2011;**96**:E1314–19. <https://doi.org/10.1210/jc.2011-0038>.
 - 96 Senda M, Ogawa S, Nako K, Okamura M, Sakamoto T, Ito S. The glucagon-like peptide-1 analog liraglutide suppresses ghrelin and controls diabetes in a patient with Prader-Willi syndrome. *Endocr J.* 2012;**59**:889–94. <https://doi.org/10.1507/endocrj.ej12-0074>.
 - 97 Salehi P, Hsu I, Azen CG, Mittelman SD, Geffner ME, Jeandron D. Effects of exenatide on weight and appetite in overweight adolescents and young adults with Prader-Willi syndrome. *Pediatr Obes.* 2017;**12**:221–28. <https://doi.org/10.1111/ijpo.12131>.
 - 98 Candler T, McGregor D, Narayan K, Moudiotis C, Burren CP. Improvement in glycaemic parameters using SGLT-2 inhibitor and GLP-1 agonist in combination in an adolescent with diabetes mellitus and Prader-Willi syndrome: a case report. *J Pediatr Endocrinol Metab.* 2020;**33**:951–55. <https://doi.org/10.1515/jpem-2019-0389>.
 - 99 Kim YM, Lee YJ, Kim SY, Cheon CK, Lim HH. Successful rapid weight reduction and the use of liraglutide for morbid obesity in adolescent Prader-Willi syndrome. *Ann Pediatr Endocrinol Metab.* 2020;**25**:52–56. <https://doi.org/10.6065/apem.2020.25.1.52>.
 - 100 Goldman VE, Naguib MN, Vidmar AP. Anti-obesity medication use in children and adolescents with Prader-Willi syndrome: case review and literature search. *J Clin Med.* 2021;**10**:4540. <https://doi.org/10.3390/jcm10194540>.
 - 101 Ng NBH, Low YW, Rajgor DD, Low JM, Lim YY, Loke KY, et al. The effects of glucagon-like peptide (GLP)-1 receptor agonists on weight and glycaemic control in Prader-Willi syndrome: a systematic review. *Clin Endocrinol (Oxf)*. 2022;**96**:144–54. <https://doi.org/10.1111/cen.14583>.
 - 102 Ahmed S, Naz A, K M. Weight loss of over 100 lbs in a patient of Prader-Willi syndrome treated with glucagon-like peptide-1 (GLP-1) agonists. *Cureus.* 2023;**15**:e35102. <https://doi.org/10.7759/cureus.35102>.
 - 103 Diene G, Angulo M, Hale PM, Jepsen CH, Hofman PL, Hokken-Koelega A, et al. Liraglutide for weight management in children and adolescents with Prader-Willi syndrome and obesity. *J Clin Endocrinol Metab.* 2022;**108**:4–12. <https://doi.org/10.1210/clinem/dgac549>.
 - 104 Sani E, Prato GD, Zenti MG, Bordugo A, Trombetta M, Bonora E, et al. Effects of semaglutide on glycemic control and weight loss in a patient with Prader-Willi syndrome: a case report. *Endocr Metab Immune Disord Drug Targets.* 2022;**22**:1053–57. <https://doi.org/10.2174/1871530322666220509225637>.
 - 105 Dinoi E, Daniele G, Michelucci A, Baldinotti F, Campi F, Marchetti P, et al. Efficacy and safety of once-weekly semaglutide monotherapy in a young subject with Prader-Willi syndrome, obesity, and type 2 diabetes: a case report. *Front Endocrinol (Lausanne)*. 2025;**16**:1533209. <https://doi.org/10.3389/fendo.2025.1533209>.
 - 106 Gimenez-Palop O, Romero A, Casamitjana L, Pareja R, Rigla M, Caixàs A. Effect of semaglutide on weight loss and glycaemic control in patients with Prader-Willi syndrome and type 2 diabetes. *Endocrinol Diabetes Nutr (Engl Ed)*. 2024;**71**:83–87. <https://doi.org/10.1016/j.endien.2023.12.001>.
 - 107 Koceva A, Mlekus Kozamernik K, Janez A, Herman R, Ferjan S, Jensterle M. Long-term efficacy and safety of semaglutide in the treatment of syndromic obesity in Prader-Willi syndrome: case series and literature review. *Front Endocrinol (Lausanne)*. 2024;**15**:1528457. <https://doi.org/10.3389/fendo.2024.1528457>.
 - 108 Ahmed S, Bridges N, Goldstone AP. Efficacy and safety of semaglutide for obesity and hyperphagia in adults with

- Prader-Willi syndrome. *Front Endocrinol.* 2026;**17**:1881392. <https://doi.org/10.3389/fendo.2026.1881392>.
- 109 Lingvay I, Bergenheim SJ, Buse JB, Herman R, Ferjan S, Jensterle M. Once-weekly semaglutide 7.2 mg in adults with obesity and type 2 diabetes (STEP UP T2D): a randomised, controlled, phase 3b trial. *Lancet Diabetes Endocrinol.* 2025;**13**:935–48. [https://doi.org/10.1016/S2213-8587\(25\)00225-6](https://doi.org/10.1016/S2213-8587(25)00225-6).
 - 110 Wharton S, Freitas P, Hjelmæsaeth J, Kabisch M, Kandler K, Lingvay I, et al. Once-weekly semaglutide 7.2 mg in adults with obesity (STEP UP): a randomised, controlled, phase 3b trial. *Lancet Diabetes Endocrinol.* 2025;**13**:949–63. [https://doi.org/10.1016/S2213-8587\(25\)00226-8](https://doi.org/10.1016/S2213-8587(25)00226-8).
 - 111 Lingvay I, Agarwal S. A revolution in obesity treatment. *Nat Med.* 2023;**29**:2406–8. <https://doi.org/10.1038/s41591-023-02563-1111>.
 - 112 Aronne LJ, Horn DB, le Roux CW, Ho W, Falcon BL, Gomez Valderas E, et al. Tirzepatide as compared with semaglutide for the treatment of obesity. *N Engl J Med.* 2025;**393**:26–36. <https://doi.org/10.1056/NEJMoa2416394>.
 - 113 Zufry H, Hariyanto TI. Head-to-head comparison of tirzepatide and semaglutide for weight loss: a systematic review and meta-analysis. *Obes Res Clin Pract.* 2026;**20**(2):92–102. <https://doi.org/10.1016/j.orcp.2026.02.002>.
 - 114 Høybye C, Barkeling B, Naslund E, Thorén M, Hellstrom PM. Eating behavior and gastric emptying in adults with Prader-Willi syndrome. *Ann Nutr Metab.* 2007;**51**:264–69. <https://doi.org/10.1159/000105447>.
 - 115 Arenz T, Schwarzer A, Pfluger T, Koletzko S, Schmidt H. Delayed gastric emptying in patients with Prader-Willi syndrome. *J Pediatr Endocrinol Metab.* 2010;**23**:867–71. <https://doi.org/10.1515/jpem.2010.140>.
 - 116 Stevenson DA, Heinemann J, Angulo M, Butler MG, Loker J, Rupe N, et al. Gastric rupture and necrosis in Prader-Willi syndrome. *J Pediatr Gastroenterol Nutr.* 2007;**45**:272–74. <https://doi.org/10.1097/MPG.0b013e31805b82b5>.
 - 117 Wharton RH, Wang T, Graeme-Cook F, Briggs S, Cole RE. Acute idiopathic gastric dilatation with gastric necrosis in individuals with Prader-Willi syndrome. *Am J Med Genet.* 1997;**73**:437–41. [https://doi.org/10.1002/\(sici\)1096-8628\(19971231\)73:4<437::aid-ajmg12>3.0.co;2-s](https://doi.org/10.1002/(sici)1096-8628(19971231)73:4<437::aid-ajmg12>3.0.co;2-s).
 - 118 Blat C, Busquets E, Gili T, Caixàs A, Gabau E, Corripio R. Gastric dilatation and abdominal compartment syndrome in a child with Prader-Willi syndrome. *Am J Case Rep.* 2017;**18**:637–40. <https://doi.org/10.12659/ajcr.903608>.
 - 119 Butler MG, Manzardo AM, Heinemann J, Loker C, Loker J. Causes of death in Prader-Willi syndrome: Prader-Willi Syndrome Association (USA) 40-year mortality survey. *Genet Med.* 2017;**19**:635–42. <https://doi.org/10.1038/gim.2016.178>.
 - 120 Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY et al. Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics.* 1993;**91**:398–402. <https://doi.org/10.1542/peds.91.2.398>.
 - 121 Gross RD, Gisser R, Cherpes G, Hartman K, Maheshwary R. Subclinical dysphagia in persons with Prader-Willi syndrome. *Am J Med Genet A.* 2017;**173**:384–94. <https://doi.org/10.1002/ajmg.a.38015>.
 - 122 Naslund E, Gutniak M, Skogar S, Rössner S, Hellström PM. Glucagon-like peptide 1 increases the period of postprandial satiety and slows gastric emptying in obese men. *Am J Clin Nutr.* 1998;**68**:525–30. <https://doi.org/10.1093/ajcn/68.3.525>.
 - 123 Naslund E, Bogefors J, Skogar S, Grybäck P, Jacobsson H, Holst JJ, et al. GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans. *Am J Physiol.* 1999;**277**:R910–16. <https://doi.org/10.1152/ajpregu.1999.277.3.R910>.
 - 124 Flint A, Raben A, Ersboll AK, Holst JJ, Astrup A. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. *Int J Obes Relat Metab Disord.* 2001;**25**:781–92. <https://doi.org/10.1038/sj.ijo.0801627>.
 - 125 DeFronzo RA, Okerson T, Viswanathan P, Guan X, Holcombe JH, MacConell L. Effects of exenatide versus sitagliptin on postprandial glucose, insulin and glucagon secretion, gastric emptying, and caloric intake: a randomized, cross-over study. *Curr Med Res Opin.* 2008;**24**:2943–52. <https://doi.org/10.1185/03007990802418851>.
 - 126 van Can J, Sloth B, Jensen CB, Flint A, Blaak EE, Saris WH. Effects of the once-daily GLP-1 analog liraglutide on gastric emptying, glycaemic parameters, appetite and energy metabolism in obese, non-diabetic adults. *Int J Obes (Lond).* 2014;**38**:784–93. <https://doi.org/10.1038/ijo.2013.162>.
 - 127 Hjerpested JB, Flint A, Brooks A, Axelsen MB, Kvist T, Blundell J. Semaglutide improves postprandial glucose and lipid metabolism, and delays first-hour gastric emptying in subjects with obesity. *Diabetes Obes Metab.* 2018;**20**:610–19. <https://doi.org/10.1111/dom.13120>.
 - 128 Modi R, Rye P, Cawsey S, Birch DW, Sharma AM. Liraglutide effects on upper gastrointestinal investigations: implications prior to bariatric surgery. *Obes Surg.* 2018;**28**:2113–16. <https://doi.org/10.1007/s11695-018-3249-1>.
 - 129 Sherwin M, Hamburger J, Katz D, DeMaria S Jr. Influence of semaglutide use on the presence of residual gastric solids on gastric ultrasound: a prospective observational study in volunteers without obesity recently started on semaglutide. *Can J Anaesth.* 2023;**70**:1300–1306. <https://doi.org/10.1007/s12630-023-02549-5>.
 - 130 Camilleri M, Carlson P, Dilmaghani S. Prevalence and variations in gastric emptying delay in response to GLP-1 receptor agonist liraglutide. *Obesity (Silver Spring).* 2024;**32**:232–33. <https://doi.org/10.1002/oby.23941>.
 - 131 Ali SN, Bridges N, Al-Nahhas A, et al. Assessing gastric emptying before and after introduction of GLP-1 agonists for glycaemic and body weight control in Prader-Willi syndrome. *Obesity (Silver Spring).* 2013;**21**(Suppl 2): S344–45.
 - 132 Sinnema M, Maaskant MA, van Schroyen Lantman-de Valk HM, van Nieuwpoort IC, Drent ML, Curfs LM, et al. Physical health problems in adults with Prader-Willi syndrome. *Am J Med Genet A.* 2011;**155A**:2112–24. <https://doi.org/10.1002/ajmg.a.34171>.
 - 133 Laurier V, Lapeyrate A, Copet P, Demeer G, Silvie M, Bieth E, et al. Medical, psychological and social features in a large cohort of adults with Prader-Willi syndrome. *J Intellect Disabil Res.* 2015;**59**:411–21. <https://doi.org/10.1111/jir.12140>.
 - 134 Kuhlmann L, Joensson IM, Froekjaer JB, Krogh K, Farholt S. A descriptive study of colorectal function in adults with Prader-Willi syndrome: high prevalence of constipation. *BMC Gastroenterol.* 2014;**14**:63. <https://doi.org/10.1186/1471-230X-14-63>.

- 135 Takrori E, Peshin S, Singal S. Gastrointestinal adverse effects of anti-obesity medications in non-diabetic adults: a systematic review. *Medicina (Kaunas)*. 2025;**61**:1987. <https://doi.org/10.3390/medicina61111987>.
- 136 Mehrtash F, Dushay J, Manson JE. I am taking a GLP-1 weight-loss medication—what should I know? *JAMA Intern Med*. 2025;**185**:1180. <https://doi.org/10.1001/jamainternmed.2025.1133>.
- 137 Mehrtash F, Dushay J, Manson JE. Integrating diet and physical activity when prescribing GLP-1s: lifestyle factors remain crucial. *JAMA Intern Med*. 2025;**185**:1151–52. <https://doi.org/10.1001/jamainternmed.2025.1794>.
- 138 Saha B, Kamalumpundi V, Codipilly DC. GLP-1 and GIP receptor agonists: effects on the gastrointestinal tract and management strategies for primary care physicians. *Mayo Clin Proc*. 2025;**S0025-6196**:00551–58. <https://doi.org/10.1016/j.mayocp.2025.09.017>.
- 139 Cowen N, Bhatnagar A. The potential role of activating the ATP-sensitive potassium channel in the treatment of hyperphagic obesity. *Genes (Basel)*. 2020;**11**:450. <https://doi.org/10.3390/genes11040450>.
- 140 Bischof JM, Wevrick R. Chronic diazoxide treatment decreases fat mass and improves endurance capacity in an obese mouse model of Prader-Willi syndrome. *Mol Genet Metab*. 2018;**123**:511–17. <https://doi.org/10.1016/j.ymgme.2018.02.018>.
- 141 Salehi P, Charlton W, Cowen NM. Pharmacokinetics of diazoxide choline controlled-release tablets, a once-a-day treatment being evaluated in patients with Prader-Willi syndrome. Presented at: 57th annual meeting of the European Society for Pediatric Endocrinology, Athens, Greece; 2018.
- 142 Miller JL, Gevers E, Bridges N, Yanovski JA, Salehi P, Obrynba KS, et al. Diazoxide choline extended-release tablet in people with Prader-Willi syndrome: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab*. 2023;**108**(7):1676–85. <https://doi.org/10.1210/clinem/dgad014>.
- 143 Miller JL, Gevers E, Bridges N, Yanovski JA, Salehi P, Obrynba KS, et al. Diazoxide choline extended-release tablet in people with Prader-Willi syndrome: results from long-term open-label study. *Obesity (Silver Spring)*. 2024;**32**:252–61. <https://doi.org/10.1002/oby.23928>.
- 144 Strong TV, Miller JL, McCandless SE, Gevers E, Yanovski JA, Mateševac L, et al. Behavioral changes in patients with Prader-Willi syndrome receiving diazoxide choline extended-release tablets compared to the PATH for PWS natural history study. *J Neurodev Disord*. 2024;**16**:22. <https://doi.org/10.1186/s11689-024-09536-x>.
- 145 Miller JL, Bridges N, Felner E, Salehi P, Yanovski JA, Stevenson DA, et al. Diazoxide choline extended-release tablets in Prader-Willi syndrome: a randomized, double-blind, withdrawal period study. *J Clin Endocrinol Metab*. 2026;**111**(6):e1554–61. <https://doi.org/10.1210/clinem/dgaf661>.
- 146 Markham A. Setmelanotide: first approval. *Drugs*. 2021;**81**(3):397–403. <https://doi.org/10.1007/s40265-021-01470-9>.
- 147 Beauloye V, Diene G, Kuppens R, Zech F, Winandy C, Molinas C, et al. High unacylated ghrelin levels support the concept of anorexia in infants with Prader-Willi syndrome. *Orphanet J Rare Dis*. 2016;**11**(1):56. <https://doi.org/10.1186/s13023-016-0440-0>.
- 148 Kuppens RJ, Diène G, Bakker NE, Molinas C, Faye S, Nicolino M, et al. Elevated ratio of acylated to unacylated ghrelin in children and young adults with Prader-Willi syndrome. *Endocrine*. 2015;**50**(3):633–42. <https://doi.org/10.1007/s12020-015-0614-x>.
- 149 Allas S, Caixàs A, Poitou C, Coupaye M, Thuilleaux D, Lorenzini F, et al. AZP-531, an unacylated ghrelin analog, improves food-related behavior in patients with Prader-Willi syndrome: a randomized placebo-controlled trial. *PLoS ONE*. 2018;**13**(1):e0190849. <https://doi.org/10.1371/journal.pone.0190849>.
- 150 Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol*. 2007;**150**(5):613–23. <https://doi.org/10.1038/sj.bjp.0707133>.
- 151 Knani I, Earley BJ, Udi S, Nemirovski A, Hadar R, Gammal A, et al. Targeting the endocannabinoid/CB1 receptor system for treating obesity in Prader-Willi syndrome. *Mol Metab*. 2016;**5**(12):1187–99. <https://doi.org/10.1016/j.molmet.2016.10.004>.
- 152 Nguyen T, Thomas BF, Zhang Y. Overcoming the psychiatric side effects of the cannabinoid CB1 receptor antagonists: current approaches for therapeutics development. *Curr Top Med Chem*. 2019;**19**(16):1418–35. <https://doi.org/10.2174/1568026619666190708164841>.
- 153 Hwang J, Cho SY. Management of hyperphagia and obesity in Prader-Willi syndrome. *Ewha Med J*. 2023;**46**(s1):e32.
- 154 Kim YM, An JJ, Jin YJ, Rhee Y, Cha BS, Lee HC, et al. Assessment of the anti-obesity effects of the TNP-470 analog, CKD-732. *J Mol Endocrinol*. 2007;**38**(4):455–65. <https://doi.org/10.1677/jme.1.02165>.
- 155 McCandless SE, Yanovski JA, Miller J, Fu C, Bird LM, Salehi P, et al. Effects of MetAP2 inhibition on hyperphagia and body weight in Prader-Willi syndrome: a randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2017;**19**(12):1751–61. <https://doi.org/10.1111/dom.13021>.
- 156 Qiu L, Chang A, Ma R, Strong TV, Okun MS, Foote KD, et al. Neuromodulation for the treatment of Prader-Willi syndrome—a systematic review. *Neurotherapeutics*. 2024;**21**(3):e00339. <https://doi.org/10.1016/j.neurot.2024.e00339>.
- 157 Dressler MH, Choi JH, Park K, Kong SH, Park DJ, Lee HJ. Bariatric surgery in patients with Prader-Willi syndrome. *J Metab Bariatr Surg*. 2025;**14**(2):85–96. <https://doi.org/10.17476/jmbs.2025.14.2.85>.
- 158 Scheimann AO, Butler MG, Gourash L, Cuffari C, Klish W. Critical analysis of bariatric procedures in Prader-Willi syndrome. *J Pediatr Gastroenterol Nutr*. 2008;**46**(1):80–83. <https://doi.org/10.1097/01.mpg.0000304458.30294.31>.
- 159 Pedemonti B, Ceccomancini R, D'Acunti A, Stegmann J. Effectiveness of a transdisciplinary approach on hyperphagia management among patients with Prader Willi syndrome. *Endocrinol Diabetes Nutr (Engl Ed)*. 2023;**70**(5):347–51. <https://doi.org/10.1016/j.endien.2022.11.021>.

Correspondence: Charlotte Höybye, Department of Endocrinology, Karolinska University Hospital, 171 76 Stockholm, Sweden. Email: charlotte.hoybye@regionstockholm.se

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: Mean scores and per cent endorsed for Food Domain items on the Prader–Willi Syndrome Personality Questionnaire (PWSPQ) among children <10 years and youth ≥ 10 years in a cohort 6–18 years of age.

Table S2: Clinical trials with oxytocin treatment in children, adolescents and adults with PWS. ■