Review Article

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Management of Hyperphagia and Obesity in Prader–Willi Syndrome

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Prader-Willi syndrome (PWS) is a neurodevelopmental disorder caused by the absence of paternally expressed imprinted genes on chromosome 15q11–13. Individuals with PWS typically experience feeding difficulties and a lack of appetite in infancy, followed by weight gain, uncontrolled appetite, and a lack of satiety. Hyperphagia in PWS is exacerbated by impaired satiety, low energy expenditure, and intellectual difficulties, including obsessive-compulsive disorder and/or autistic behaviors. Without rigorous external management of their eating behaviors, patients with PWS become severely obese and are at a higher risk of obesity-related morbidities, such as type 2 diabetes, obstructive sleep apnea, and hypertension. Moreover, the main causes of death for PWS are obesity-related comorbidities, such as renal failure, pulmonary embolism, and respiratory and heart failure. Clinical experiences with different supplements, diets, and other methods have not been encouraging. However, therapeutic options for patients with PWS may be improving, based on recent clinical trials for a number of medications. This report reviews the causes and management of hyperphagia, as well as previous and recent clinical trials aimed at treating hyperplasia in PWS. We are optimistic that the novel treatments currently in development will help alleviate the complex metabolic issues associated with PWS.

Introduction

Prader-Willi syndrome (PWS) is a genetic disorder caused by loss of function of paternal chromosome 15 q11–q13. The paternally expressed PWS region contains genes that encode polypeptides and small nucleolar RNAs, such as *MKRN3*, *MAGEL2*, and *NECDIN* [1]. The clinical manifestations of PWS include hypotonia, early childhood-onset hyperphagia, a characteristic facial appearance, hypogonadism, growth hormone (GH) deficiency, mild-to-severe intellectual delays, and behavioral disturbances [2]. With advancements in genetic testing, PWS can now be diagnosed very early, during the neonatal period. Early diagnosis and comprehensive therapy can significantly improve the natural progression of PWS [3]. However, without rigorous management of dietary habits, individuals with PWS are prone to developing severe obesity and its associated health risks, such as type 2 diabetes (T2DM), obstructive sleep apnea, and hypertension. Complications related to obesity, including respiratory and cardiac failure, pulmonary embolism, and renal failure, are the primary causes of mortality in PWS patients. The clinical management of PWS typically involves strict dietary control and vigilant monitoring of food consumption. Currently, there are no definitive pharmacological treatments for the hyperphagia or obesity

that affect individuals with PWS. Nevertheless, clinical trials are currently investigating several medications that may offer new therapeutic options for PWS patients in the future. This study reviews the management of hyperphagia, its underlying causes, and both current and past clinical trials aimed at treating hyperphagia in PWS.

Natural Course of Hyperphagia in Prader-Willi Syndrome

The natural course of PWS is characterized by various nutritional phases, each with a distinct and complex progression, as presented in Table 1 [4]. The prenatal characteristics of phase 0 include being small for gestational age, breech presentation, polyhydramnios, decreased fetal movement, and lower birth weight compared to siblings [5]. At birth (phase 1), hypotonia is the defining characteristic. From birth to 9 months (phase 1a), poor sucking and feeding difficulties are common, often leading to failure to thrive. From birth to 24 months (phase 1b), growth typically follows a disease-specific growth chart [6,7]. During phase 2a (2–4.5 years of age), weight gain is observed, although there is no significant change in appetite. In phase 2b (ages 4.5–8), an individual's appetite and interest in food usually increase. By phase 3 (after 8 years of age), hyperphagic behaviors become evident, including aggressive food-seeking and an insatiable desire to eat. Hyperphagia significantly disrupts learning, social interactions, relationships, work productivity, and overall quality of life [8]. Some adults reach phase 4, where the increased appetite subsides; however, most individuals with PWS do not experience this phase. As the nutritional stages advance, various behavioral and endocrine disturbances emerge, leading to a range of comorbidities throughout the individual's lifetime.

Potential Mechanisms of Hyperphagia

Several theoretical models have been proposed to explain why people with PWS tend to overeat. These include issues with satiety rather than hunger; the impact of internal physiological awareness on hunger and satiation; hyperresponsive reward systems that liken food to a drug of abuse; the direct influence of genetics on the hypothalamic feeding pathway; and the significance of the perinatal environment [9]. Table 2 provides a summary of the pertinent findings.

Table 1. Natural course of hyperphagia in Prader-Willi syndrome

Phases	Median ages	Clinical characteristics
0	Prenatal to birth	Less activity during pregnancy and a smaller birth weight than siblings
1	At birth	Hypotonia
1a	0–9 months	Difficulty feeding and decreased appetite
1b	9–24 months	Enhanced appetite and eating; proper growth
2a	2.0–4.5 years	Gaining weight in the absence of an increase in appetite or additional calories
2b	4.5–8.0 years	Heightened interest in and hunger for meals, but feeling full
3	8 years-adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

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Table 2. Potential mechanisms causing hyperphagia in Prader-Willi syndrome (PWS)

Factor	Type of abnormality	Function	Reference
Thyroid hormone	Decreased	Regulates whole-body metabolism. In PWS: Altering metabolic rate and energy consumption as a consequence.	[57]
Ghrelin	Elevated	Temporally regulates food intake, heightens appetite, and lessens appetite after eating. In PWS: prolonged elevation of ghrelin levels, even after meals, leads to weight gain.	[58]
Leptin	Elevated	Helps regulate the body's long-term food intake and use.	[59]
Brain-derived neurotrophic factor (BDNF) and leptin	BDNF: decreased Leptin: elevated	Serves as an indicator of fullness. In PWS: local BDNF levels decrease as a result of a disruption in BDNF signaling, which boosts leptin levels and leads to leptin resistance, ultimately resulting in obesity and hyperphagia.	[60]
Insulin	Decreased	Activates melanocortin-4 receptor (MC4R) and cause satiety, stimulates Pro-opiomelanocortin (POMC) and inhibits Neuropeptide Y (NPY) neurons. In PWS: decreased insulin causes MC4R not to be stimulated.	[61]
Peptide YY	Decreased	Induces satiety by decreasing stomach emptying and activating α and β-Melanocyte-stimulating hormone(MSH) through the inhibition of NPY and stimulation of POMC. In PWS: reduced PYY stops stimulating α- and β-MSH and results in a decrease of stimulating signals to POMC.	[62]
Altered brain structure	Cortical volume: decreased White matter integrity: reduced fractional anisotropy Gray matter volume: decreased	Reduced cortical volume in the bilateral frontal, medial prefrontal cortex, and anterior cingulate causes imbalances in cognitive and emotional processing, which in turn causes appetite management dysfunctions, elevated self-reported hunger, and an increased risk of overeating. White matter function decreases in proportion to the fractional anisotropy decrease. The PWS brain areas linked to food consumption showed abnormalities in both the white and gray matter.	[63]
Orexin A	Elevated	Boosts food consumption and stimulates appetite. In PWS: the hypothalamus overstimulates orexin signaling, which exacerbates food addiction and leads to hyperphagia.	[64]

Obesity and Related Comorbidities in Prader-Willi Syndrome

In individuals with PWS, obesity is a primary contributor to early morbidity and mortality [10]. The rate of obesity varies among PWS patients, with different age groups showing different prevalence rates. In children and adolescents, the prevalence of obesity has been reported to be 40% [11]. This prevalence increases to between 82% and 98% in adult PWS patients, depending on the cohort studied [12]. Reduced sleep duration and longer sitting times are strongly linked to a higher risk of overweight or obesity [13].

Pulmonary embolism, respiratory failure, pulmonary hypertension, obstructive sleep apnea, right heart malfunction, steatohepatitis, gallstones, deep venous thrombosis, and chronic leg edema are among the comorbidities frequently linked to obesity in PWS [10,14–16]. These comorbidities can lead to potentially fatal conditions. For example, a case study reported a 21-year-old man with PWS who became severely obese and developed obstructive sleep apnea, which led to cor pulmonale—a potentially life-threatening outcome [17]. Respiratory and cardiac disorders account for 38% and 16% of deaths in PWS, respectively [16].

Obesity is linked to a markedly higher prevalence of metabolic syndrome (MS) and cardiometabolic risk factors [18]. Studies indicate that hyperlipidemia is present in approximately one-third of individuals with PWS [19]. Low high-density lipoprotein cholesterol levels and abdominal obesity, which are components of MS, were found to be strongly associated with high-sensitivity

C-reactive protein levels in Korean children and adolescents [20]. MS not only potentially contributes to the high mortality rate in PWS but is also a major risk factor for T2DM and atherosclerotic cardiovascular disease. The general guidelines for managing obese adolescents are similar to those for diagnosing, treating, and screening T2DM and MS. First-line treatments include intensive dietary counseling and regular physical activity. Metformin may be used as an adjunct therapy [21]. Regular insulin administration is also necessary, depending on the hemoglobin A1c level [22]. Pediatric endocrinologists often face challenges in providing transitional care for patients with T2DM [23].

Current Standard Therapies

GH treatment is currently part of the routine care for people with PWS during their youth. [24]. GH treatment may reduce insulin sensitivity regardless of obesity status; however, short-term trials have not demonstrated changes in hemoglobin A1c levels [25]. Although patients with PWS who receive GH treatment remain obese, long-term observational studies have shown improvements in body composition and body mass index [26].

Nutritional counseling plays a crucial role in preventing excessive weight gain, and studies show that with early nutritional management, children can attain a normal body mass [27]. Infants and children with PWS typically require only 60% to 80% of the standard daily caloric intake because of their reduced resting energy expenditure, which helps maintain a stable body weight [28,29].

An energy-restricted, well-balanced diet consisting of 30% fat, 45% carbohydrates, 25% protein, and at least 20 g of fiber daily can help prevent excessive weight gain and fat accumulation in children with PWS, typically starting at 2 years of age [30]. From an early age, children should be accustomed to drinking plain water, and parents should avoid offering sweetened beverages. Reducing sugar intake early in life can decrease the propensity to overeat. Additionally, individuals with PWS are advised to adhere to a Mediterranean diet, which is rich in complex carbohydrates, fruits, vegetables, legumes, nuts, and oils, while being low in meat and predominantly plant-based [31]. Portion sizes should be carefully regulated in relation to the individual's physical activity level and weight management goals.

Regular weighing, portion control, implementing barriers to food access (such as locking cabinets, refrigerators, and/or kitchens to deter food theft), along with dietary and financial restrictions, are additional weight-management strategies. Locking pantries, refrigerators, and food cabinets should be considered only when there is clear evidence of someone searching for food. For individuals with PWS, knowing that food is secure and not a source of temptation can be incredibly beneficial, even though such measures may appear unfair and archaic. Children with PWS need the support of educators, grandparents, caregivers, and family friends to adhere to recommended diets, eating schedules, healthy eating practices, and regular physical activity. Exercise should be considered a daily requirement beginning at a young age. The relationship between individuals with PWS and their coaches, therapists, dietitians, or doctors is a critical factor in determining the success of adherence to and maintenance of various activities, such as exercise and dietary modifications [32].

Potential Pharmaceutical Treatments for Reducing Hyperphagia

Several pharmaceutical companies have attempted to develop drugs to target the mecha-

nisms of PWS (Table 3).

1. Oxytocin

The neuropeptide hormone oxytocin is involved in social interactions, eating habits, anxiety, energy expenditure, maternal behaviors, and controlling body weight [33,34], all of which are negatively impacted by PWS. PWS patients have fewer oxytocin-producing neurons in the hypothalamic periventricular nuclei [35]. Therefore, multiple clinical studies have investigated the use of oxytocin to treat PWS (Table 3).

Intranasal oxytocin was found to be ineffective in treating hyperphagia and body weight in a group of 92 individuals with PWS, according to a comprehensive review and meta-analysis. The outcomes were comparable to those observed with a placebo [36]. The lack of positive results from oxytocin treatment in the analyzed trials may be attributed to variations in dosage and administration methods. However, this does not conclusively indicate that oxytocin is ineffective

Table 3. Potential treatments to reduce hyperphagia in Prader-Willi syndrome (PWS)

Mechanism of action	Reason for treatment selection	Studies
Oxytocin The brain produces the neuropeptide hormone oxytocin, which is involved in eating behavior, anxiety, energy expenditure, controlling body weight, and social interactions.	It has been noted that PWS patients have fewer neurons that produce oxytocin. Their inability to control their emotions, bad eating habits, and poor social integration may all be related to this deficiency.	[65–72]
Diazoxide choline-controlled release (DCCR) DCCR, a benzothiadiazine, is used to treat hyperinsulinemia-related hypoglycemia in newborns, children, and adults by increasing ion flow through ATP-sensitive K^+ channels.	The dysregulation of neuropeptide Y/Agouti-related protein/gamma-aminobutyric acid (NAG) neurons, which are regulated by leptin by decreasing their excitability, is linked to hyperphagia in Parkinson's disease. The most powerful endogenous neuropeptide, Neuropeptide Y (NPY), is produced and secreted in significant amounts as a result of this imbalance. The hyperpolarization of the resting membrane potential caused by leptin's activation of ATP-sensitive K^+ channels (KATP) via phosphoinositide-3-kinase (PI3-K) limits the release of NPY by these neurons, thereby attenuating the hyperphagia signal.	[39]
Glucagon-like peptide-1 agonist During meals, the pancreas secretes more insulin in response to food consumption, which aids in controlling postprandial glucose levels. The synthesis of glucagon-like peptide-1 (GLP-1) aids in this process.	Studies have investigated how GLP-1 receptor agonists, which delay stomach emptying and decrease appetite, impact weight loss.	[42–44]
Setmelanotide Setmelanotide, an agonist of the melanocortin (MC)-4 receptor, influences feeding and satiety to decrease eating.	Patients with PWS show strong food desire and hyperphagia from an early age, and eventually develop excessive obesity if their condition is not treated externally.	[45–47]
Livoletide Livoletide is an inactive analog of ghrelin that works by lowering the amount of the active form of ghrelin in the brain. The stomach produces a neuropeptide known as ghrelin, which triggers the human hypothalamus to directly stimulate appetite.	PWS patients have higher ghrelin levels.	[48–50,69]
Cannabinoids The control of appetitive behavior is significantly influenced by the cannabinoid-1 receptor (CB1R).	Cannabinoids have an anti-obesity effect because of their antagonistic impact on CB1R.	[51]
Beloranib In animal models, beloranib inhibits methionine aminopeptidase 2 (MetAP2) by removing methionine residues from proteins, thereby impacting adipocyte development and fat metabolism.	It has been discovered that MetAP2 inhibitors lower food intake, impact adipose tissue, and decrease fat production during weight reduction in people.	[73]
Transcranial direct-current stimulation (tDCS) tDCS is a method of modifying neural and cognitive performance in specific brain regions to help control food cravings. It is painless, safe, and non-invasive.	The dorsolateral prefrontal cortex is a brain region that mediates the processing and regulation of human food appetites and motivation.	[53–55]

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in treating hyperphagia and behavioral abnormalities, which are two symptoms of PWS. To determine the efficacy of oxytocin in PWS patients more conclusively, further large-scale prospective randomized controlled trials are necessary.

2. Carbetocin

An analog of oxytocin, intranasal carbetocin, has been explored as a targeted therapy for oxytocin replacement and has shown promising effects on hyperphagia [37]. A phase III trial, which was randomized, double-blind, placebo-controlled, and included long-term follow-up, involved 130 patients with PWS aged 7 to 18. These participants were recruited from 24 outpatient clinics at academic medical centers [38]. They were randomized to receive either 9.6 mg/dose of carbetocin, 3.2 mg/dose of carbetocin, or a placebo three times daily for 8 weeks. During the subsequent 56-week long-term follow-up, those initially on placebo were reassigned to either the 9.6 mg or 3.2 mg carbetocin dose. The onset of the coronavirus disease 2019 (COVID-19) pandemic led to the early termination of enrollment. The Hyperphagia Questionnaire for Clinical Trials (HQ-CT) and the Children's Yale-Brown Obsessive-Compulsive Scale showed numerical improvements in the 9.6-mg group, but these did not reach statistical significance. In contrast, the 3.2-mg group showed marginally significant improvements compared to placebo on the HQ-CT, the PWS Anxiousness and Distress Behaviors Questionnaire, and the Clinical Global Impression of Change. The most common adverse effect was flushing, ranging from mild to severe. Consequently, carbetocin was well-tolerated, and a 3.2-mg dose was associated with clinically meaningful improvements in hyperphagia, anxiety, and distress behaviors in patients with PWS.

3. Diazoxide choline controlled-release

Diazoxide choline, a benzothiadiazine, activates ion flow through ATP-sensitive K^+ channels (KATP). It is currently used to treat hypoglycemia and hyperinsulinemia. In the adipocytes of patients with PWS, diazoxide may exert a therapeutic effect by stimulating KATP channels, modulating hypothalamic neuropeptide Y, and affecting insulin secretion from pancreatic β-cells [39]. An oral, once-daily, extended-release tablet of diazoxide choline controlled-release (DCCR) has been developed. A 12-week course of oral DCCR treatment has been shown to reduce blood glucose levels, decrease fat mass, and improve endurance [40]. A phase 3 trial involving 127 PWS patients aged 4 years and older with hyperphagia, was conducted over 13 weeks. This double-blind, placebo-controlled study randomly assigned participants in a 2:1 ratio to receive either DCCR or a placebo [41]. The primary outcome measure was the change in hyperphagia from baseline, as assessed by the HQ-CT. Secondary endpoints included the Clinical Global Impression of Change score and changes in behavior, hormones, and body composition. In the pre-COVID-19 analysis, and particularly among subjects with severe baseline hyperphagia, DCCR treatment significantly improved hyperphagia. However, the primary analysis did not show a significant improvement in hyperphagia overall.

4. Glucagon-like peptide-1 agonists

The hormone glucagon-like peptide-1 (GLP-1) is produced by the L-cells of the colon and ileum. It is released in response to food intake and enhances the pancreas's ability to secrete insulin during meals, aiding in the regulation of postprandial glucose levels. Research on the effects of GLP-1 receptor agonists on weight loss has shown that they can lead to delayed gastric emptying and a reduction in appetite [42]. A comprehensive review indicates that GLP-1

receptor agonists are generally safe for individuals with PWS and may offer benefits in managing weight, blood glucose, and satiety. However, given the inherent risk of gastric rupture in this population and the potential side effect of delayed gastric emptying, careful consideration is required when prescribing GLP-1 receptor agonists [43,44].

5. Setmelanotide

Setmelanotide is a potent and specific agonist of the melanocortin-4 receptor that is used to treat genetic disorders associated with obesity. Effective activation of melanocortin-4 receptor may help reduce the hyperphagia associated with PWS [45]. A phase II trial investigated the effects of once-daily subcutaneous injections of setmelanotide in 40 individuals with PWS (19 males and 21 females; mean age, 26.4 years) [46]. There was no significant difference in the mean weight change between the setmelanotide and placebo groups at 4 weeks. At the two highest doses of setmelanotide, there was a slight, but not statistically significant, reduction from baseline in the mean hyperphagia questionnaire score. Adverse effects included occasional mild-to-moderate injection site reactions, darkening of the skin and nevi, and sporadic, spontaneous penile erections. Although the results in PWS were not promising, subsequent studies on the effects of setmelanotide in other rare monogenic forms of obesity, such as in individuals with POMC mutations or Bardet-Biedl syndrome—a group of genetic disorders affecting ciliary proteins—were successful [47].

6. Livoletide

In PWS, hyperphagia is associated with the ratio of acylated ghrelin (AG) to unacylated ghrelin (UAG) [48]. It has been theorized that a decrease in UAG levels leads to an increased AG/UAG ratio, which may contribute to the development of hyperphagia [49]. Therefore, one potential treatment approach for hyperphagia is to pharmacologically increase UAG levels. Livoletide, also known as AZP-531, is a peptide analogue of UAG [49]. In a pivotal phase 2b/3 study, which was double-blind and placebo-controlled, 158 PWS patients were randomly assigned to receive either livoletide at a dose of 60 μg/kg or a placebo at a dose of 120 μg/kg [50]. Livoletide was generally well-tolerated throughout the study period. The most common adverse effect reported was a mild reaction at the injection site. However, livoletide did not significantly impact body weight, waist circumference, or fat mass as measured by dual-energy X-ray absorptiometry. It also failed to significantly reduce hyperphagia or food-related behaviors. Consequently, the company announced that it would discontinue the development of livoletide as a potential therapeutic option for PWS.

7. Cannabinoids

The cannabinoid-1 receptor (CB1R) plays a crucial role in regulating appetitive behavior. It is most abundantly expressed in the hypothalamus and other brain regions associated with appetite control. Cannabidiol, a non-psychotropic constituent of cannabis plants, exerts an anti-obesity effect through its antagonistic action on CB1R [51]. The CB1R blocker JD5037 interacts with cannabinoid receptors to diminish appetite and enhance satiety. Although JD5037 reached the stage of enrolling participants for an early clinical trial as a potential treatment for hyperphagia in PWS, unforeseen complications resulted in the trial's discontinuation.

8. Beloranib

Beloranib removes methionine residues from proteins, thereby inhibiting methionine amino-

peptidase 2 and influencing fat metabolism. In the United States, a large group of adults and adolescents with PWS participated in a phase III randomized, placebo-controlled, double-blind study of beloranib. Over the 26-week treatment period, the groups receiving beloranib experienced a significant decrease in fat mass compared to the placebo group, with participants achieving a weight loss of 5% or more. Additionally, those treated with beloranib demonstrated improvements in eight of the nine HQ-CT item scores. Unfortunately, the occurrence of venous thromboembolic events, including two deaths, among participants in the beloranib group necessitated the premature discontinuation of the trial.

9. Transcutaneous vagus nerve stimulation

Recently, Holland et al. [52] showed that transcutaneous vagus nerve stimulation can be an effective treatment for temper tantrums and associated behaviors in individuals with PWS and hyperphagia. Four of the five participants with PWS exhibited a significant reduction in the frequency of their outbursts. Additionally, improvements were noted in emotional regulation, responses to treatments, and the ability to manage and cope with situations that typically precipitate outbursts. However, there was no observed decrease in hyperphagia [52].

10. Transcranial direct-current stimulation

Transcranial direct-current stimulation (tDCS) is a safe, painless, and non-invasive technique that can modify neuronal and cognitive functions in targeted areas of the brain [53]. For instance, tDCS activates the dorsolateral prefrontal cortex, which is important in processing and controlling food urges [53–55]. A few studies have provided evidence that tDCS is beneficial for hyperphagic behavior in PWS patients [53]; however, further testing is required.

Surgical Management of Obesity in Prader-Willi Syndrome

Bariatric surgery remains a contentious treatment option for obesity in individuals with PWS. Scheimann et al. [56] conducted a retrospective analysis of 60 documented cases of bariatric surgery in patients with PWS, identifying a range of postoperative complications. Individuals with PWS are highly susceptible to developing gastric dilatation or necrosis due to prevalent medical issues such as hyperlipidemia, GH deficiency, increased insulin sensitivity, a reduced ability to vomit, and an atypical eating pattern characterized by hyperphagia. Consequently, compared to obese individuals without PWS, those with PWS may face a higher risk of complications from bariatric surgery. Severe incidents reported include the death of one patient following gastric and jejunoileal bypass, deep vein thrombosis and wound infection in another, and the necessity for splenectomy during bariatric surgery in two patients. Although the majority of PWS patients who undergo gastroplasty initially lose weight, they tend to regain it over time. Given the limited evidence from a few case series, it appears there is little justification for subjecting individuals with PWS to the significant potential risks associated with bariatric surgery [56].

Conclusion

Safe and effective treatment is necessary for managing both hyperphagia and obesity in patients with PWS, as the majority of affected individuals display significant food-seeking behavior and hyperphagia from early childhood. Without intervention, they often develop severe obesity over time. A variety of medications have been explored or are currently undergoing

clinical trials to address hyperphagia and obesity in PWS patients. Research has shown that several medications can ameliorate hormonal imbalances, body composition issues, and eating behaviors. However, there is scant evidence supporting the long-term safety and effectiveness of these treatments in the PWS population, highlighting the need for further study. Additionally, there is a need for more rigorous research to develop objective measures of hyperphagia, beyond the subjective questionnaires currently used in clinical trials. Through these treatments, we aim to mitigate the complex metabolic challenges associated with PWS.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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