Review

Current Treatments of Prader-Willi Syndrome: A Systematic Review

Junli Zhu, BS;[1] Xuejun Kong, MD[2]*

[1] *Fisher College, Boston, MA*
[2] *Martinos Center, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA*

Prader-Willi Syndrome (PWS) is a genetic imprinting disorder mainly caused by the absence of paternally expressed imprinted genes at 15q11.2-q13, maternal uniparental disomy (UPD) and imprinting defect. Typical features include hypotonia in early infancy, subsequent hyperphagia and morbid obesity, developmental delay and intellectual disability. The aims of this systematic review are to summarize the current knowledge of the treatments for PWS based on the clinical studies published from 2000 to 2017. We searched three main databases - PubMed, MEDLINE, and Scopus, and selected 34 out of 1139 articles initially identified for this review. We focused our discussions on the widely-accepted growth hormone (GH) treatment, and emerging investigational treatments oxytocin (OXT), anti-diabetes and anti-obesity drugs. In addition, early detection, early treatment, and combination therapies are proposed to assure a better outcome.

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INTRODUCTION

As the first recognized human genetic imprinting disorder, Prader-Willi Syndrome (PWS) has an estimated prevalence in several studied populations of 1/10,000-1/30,000.[1] This multisystem genetic disorder could be caused by the absence of paternally expressed imprinted genes at 15q11.2-q13 through paternal deletion, maternal uniparental disomy (UPD) of chromosome 15, or an imprinting defect.[2] The characteristic features of PWS include severe hypotonia in early infancy, subsequent hyperphagia and morbid obesity from early-childhood, developmental delay, mild intellectual disability, and a distinct behavioral phenotype.[1,3]

For adult patients with PWS, the leading cause of death is complications of obesity.[4] Though its etiology has remained unclear so far, the cause of hyperphagia for patients with PWS is usually considered to be hypothalamic dysfunction, which is also responsible for growth hormone (GH), sex hormone, and thyroid-stimulating hormone (TSH) deficiencies.[3,5] Current treatments for PWS include: well established clinical use of Growth Hormone (GH), and emerging new therapies such as Oxytocin (OXT), and drugs for diabetes mellitus and obesity such as Metformin, Beloranib, and GLP-1 receptor agonist. The objective of this systematic review is to summarize the most effective treatments for PWS based on clinical trials.

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***Corresponding Author:** Martinos Center, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA
149 13th street, 1117A, Charlestown, MA 02129.
(Email: xkong1@mgh.harvard.edu)

METHOD

Research Design

A systematic review protocol was developed to explore the most promising treatments for PWS. The evaluation of different categories of medications was based on the published clinical trial data.

Search Strategy

A systematic search was conducted in the following databases: PubMed, MEDLINE, and Scopus. In order to conduct a thorough systematic search about treatments for PWS, multiple searches were undertaken using the following terms: “Prader-Willi Syndrome AND/OR treatment” “Prader-Willi Syndrome AND/OR medication treatment” “Prader-Willi Syndrome AND/OR growth hormone” “Prader-Willi Syndrome AND/OR oxytocin” “Prader-Willi Syndrome AND/OR Metformin” “Prader-Willi Syndrome AND/OR GLP-1 Receptor Agonist” “prader-Willi Syndrome AND/OR Exenatide” “Prader-Willi Syndrome AND/OR Beloranib” “Prader-Willi Syndrome AND/OR Liraglutide” “Prader-Willi Syndrome AND/OR behavior treatment” “Soles of the Feet”.

1139 articles were identified after the search. After duplication removal and screening the articles with inclusion and exclusion criteria, 34 articles were included in this systematic review. (**Figure 1**)

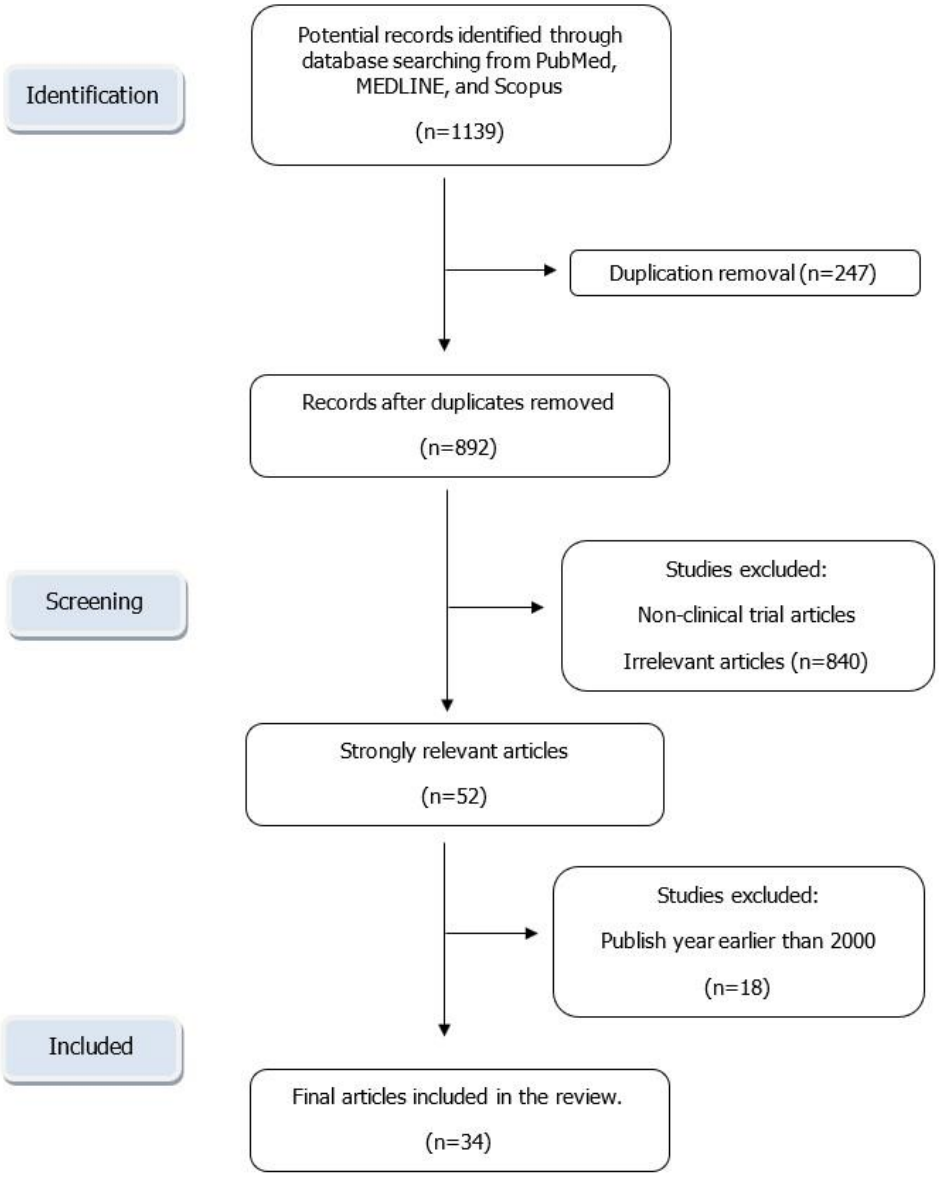

Figure 1. Flow diagram of search strategy and study selection.

Inclusion and Exclusion Criteria

Articles were included when they were: 1) English-written clinical trials (including nonrandomized open trials and randomized controlled trials); 2) studied the efficacy or effect of one or multiple treatments for PWS; and 3) published between January of 2000 and October of 2017. Studies published before 2000 or not strongly related to PWS treatments were excluded.

RESULTS

Based on the above inclusion and exclusion criteria, our final search selected 34 articles. Among these articles, twenty were reports of clinical trials studying the effect of medication treatments for PWS, whose details were showed in three tables (**Table 1-5**). The other thirteen articles focused on other treatment aspects and one focused on the stress level of caregivers, which will be presented in the following discussion section.

Growth Hormone (GH) Studies

GH is the well-established medication for PWS. We selected nine clinical trials focusing on GH after filtration.[6-14] (**Table 1, 2**)

Table 1. Chart of Clinical Trials for Growth Hormone Treatment (Characteristics).

Author(s)	Publication Year	Country of Study	Study Design	Case Number		Age Group	Length	Outcome Measure	Age Group
Bakker Et al.[6]	2017	The Netherlands	Worldwide retros-pective cohort study	Efficacy evaluation	522	4.36 ± 2.88	≥ 3 yr		
				Safety analysis	2332	6.0 ± 4.33	≥ 2 yr before puberty and until adult height	1. heightbody,BMI SDS 2. occurrence of serious adverse events 3. deaths reported in KIGS.	4.36 ± 2.88
Lecka-Ambroziak Et al.[7]	2017	Poland	Case control study	36		7.98	-	1. nasal respiratory flow (by PSG) 2. respiratory effort 3. blood oxygen saturation	7.98
Kupens Et al.[8]	2016	The Netherlands	Randomized, double-blind, placebo-controlled crossover study	27		17.2	2 years	1. blood pressure 2. TC,LDLc and HDLc 3. triglyceride (TG) 4. GF-I,IGFBP-3, and OGTT	17.2
Butler Et al.[9]	2013	U.S.	One-Group Designs	11		32	2 years	1. Electrolytes, IGF-I, glucose, thyroid, insulin, lipids. 2. body composition 3. physical activity and strength 4. diet, energy expenditure and quality of life data	32
Sode-Carlsen Et al.[10]	2010	Denmark	Randomized, double-blind, placebo-controlled study	46		28.7	18 months	Body composition (measured by computed tomography and dual-energy x-ray absorptiometry)	28.7
Carrel Et al.[11]	2010	U.S.	Observational study	48		5–9	-	1. Percent body fat 2. lean body mass 3. carbohydrate/lipid metabolism 4. motor strength (compared using analysis of covarianc)	5–9
Gondoni Et al.[12]	2008	Italy	One-Group Designs	12		26.4±4.4	12 months	1. Body composition (measured by Dual Energy X-ray Absorptiometry) 2. physical performance (evaluated using treadmill exercise test)	26.4±4.4
HoybyeEt al.[13]	2007	Sweden	Cohort study	14		median age 31	6 Years	Body composition (measured by Dual Energy X-ray absorptiometry)	Body composition (measured by Dual Energy X-ray absorptiometry)
Hoybye Et al.[14]	2003	Sweden	Randomized placebo-controlled clinical trial	19		17-32	2 years	1. Body composition (using dual energy X-ray absorptiometry) 2. metabolic and endocrinological parameters (OGTT)	1. Body composition (using dual energy X-ray absorptiometry) 2. metabolic and endocrinological parameters (OGTT)

Table 2. Chart of Clinical Trials for Growth Hormone Treatment (Results).

Authors	Results							
	Height	Lean body mass	Body fat	Appetite	BMI	LDL	HDL	Others
Bakker Et al.[6]	completely normalized	-	-	-	increased	-	-	-
	increase 0.95 SDS	-	-	-	No change	-	-	No increase in mortality rate
Lecka-Ambroziak Et al.[7]	-	-	-	-	-	-	-	oxygen desaturation index increased in short-term group
Kupens, Et al.[8]	-	-	-	-	-	No change	No change	increased fasting glucose and insulin
Butler, Et al.[9]	-	increased	decreased	-	-	-	increased	1.increased IGF-I levels and improved energy expenditure
Sode-Carlsen Et al.[10]	-	increased	decreased	-	-	-	-	increased IGF-I
Carrel, Et al.[11]	increased	-	decreased	-	-	decreased	increased	greater motor strength and sit-ups
Gondoni, Et al.[12]	-	increased	decreased	-	-	-	-	Attained metabolic equivalents improved
Hoybye, Et al.[13]	-	increased	non-significantly decreased of 5%	-	-	-	-	-
Hoybye, Et al.[14]	-	increased	decreased	-	-	-	-	body composition changes in PWS genotype.
Bakker, Et al.[6]	completely normalized	-	-	-	increased	-	-	-
	increase 0.95 SDS	-	-	-	No change	-	-	No increase in mortality rate
Lecka-Ambroziak Et al.[7]	-	-	-	-	-	-	-	oxygen desaturation index increased in short-term group
Kupens Et al.[8]	-	-	-	-	-	No change	No change	increased fasting glucose and insulin

Among these nine studies, six were published between 2010 and 2017, and the other three were published between 2000 and 2010. These studies focused on the effects of GH treatment on the body composition and metabolic index of affected individuals with PWS. In six out of nine studies, patients have either reduced body fat percent or increased lean body mass significantly, covered the age group from age 5 to 30s, treatment time from 12 months to 6 years, two of them were randomized trials.[9-14] Among these trials, there is a large-scale retrospective cohort study, average age 4-6, with treatments of 3 years or longer. It reports significant height improvement after the treatment.[6] Greater motor strength was reported in one study.[11] Lipid profile HDL and LDL were tested in three trials, and two of them showed decreased LDL and increased HDL.[8,9,11] These studies showed no significant adverse effect or safety issue with the treatments except transient blood sugar elevation in one study, and 12 deaths out of 2332 safety analysis in the retrospective cohort, which was lower than the reported 3% annual mortality rate in patients with PWS.[6]

Oxytocin (OXT) Studies

Four studies on OXT published between 2011 and 2017 were selected. (**Table 3**)

Effects of OXT treatment on the behaviors of patients with PWS were mainly investigated. Three of the studies showed behavioral improvements after OXT treatment, which included less food-related behavior, decreased sadness and anger tendencies, increased trust in others and improved social behaviors. However, one out of the four studies showed no significant change.[17] There was only one study showed a modest increase in height after treatment.16 Meanwhile, none of those studies showed any significant changes in BMI, even though a reported appetite decrease in two studies.[15,16]

Table 3. Chart of Clinical Trials for Oxytocin.

Author(s)		**Miller Et al.[15]**	**Kuppens Et al.[16]**	
Publication Year		2017	2016	
Country of Study		U.S.	The Netherlands	
Study Design		Double-blind, placebo-controlled, crossover study	Randomized, double-blind, controlled crossover trial	
Age Group		5 Years to 11 Years	6 to 11 years	11 to 14 years
Case Number		24	17	8
Length		6 weeks	4 weeks	
Outcome Measure		1. Questionnaires 2. blood testing	1. Height, BMI, percentage fat (measured by DXA)	
Results	Height	-	increased	increased
	BMI	-	No significant change	No significant change
	behaviroal parameters	improved socialization, anxiety, and repetitive behaviors	improved anger, sadness and conflicts	happiness, anger and sadness were negatively influenced
	Appetite	decreased	decreased	no changes
	Others	1.All scales factor improvement from Day 3 to Day 6 favored oxytocin over placebo. 2.No single factor showed a statistically significant difference between groups at Day 6.	-	-

Author(s)		**Einfeld Et al.[17]**	**Tauber Et al.[18]**	
Publication Year		2014	2011	
Country of Study		Australia	France	
Study Design		Double-blind randomized controlled trial	Double-blind, randomised, placebo-controlled study	
Age Group		12-30 years	18.7 to 43.6 years with median age 28.5	
Case Number		30	24	
Length		18 weeks	-	
Outcome Measure		Questionaires	Behaviours (scored by psychologis using an in-house grid)	
Results	Height	-	-	
	BMI	-	-	
	behaviroal parameters	increased trust decreased sadness,disruptive behaviour,less conflict -	increased trust decreased sadness,disruptive behaviour,less conflict -	happiness, anger and sadness were negatively influenced
	Appetite	no changes	-	
	Others	-	-	

Table 4. Chart of Clinical Trials for Diabetes and Obesity Drugs (Characteristics).

Authors	Publication Year	Country of Study	Medication	Study Design	Case Number	Age Group	Length	Outcome Measure
Salehi Et al.[19]	2017	U.S.	Exenatide	Open-label, non-randomized, longitudinal, single group assignment study	10	13-25	6 months	1. Weight, BMI 2. truncal fat 3. appetite 4. plasma acylated ghrelin
Sze Et al.[20]	2011	Australia	Exenatide	Single-blinded, randomized, crossover design study	19	30.8	2 weeks	1. Glucose, insulin, glucagon 2. peptide YY, glucagon-like peptide-1, ghrelin 3. appetite 4. energy expenditure
Fintini Et al.[21]	2014	Italy	GLP-1 Receptor Agonist (Liraglutide/Exenatide)	Case report	6	20.7–37.7	24 months	1. BMI, waist circumference. 2. metabolic parameters
Senda Et al.[22]	2012	Japan	Liraglutide	Case report	1	25	-	1. plasma levels of insulin and eptin,adiponectin (high molecular), GLP-1 (active) and ghrelin (active) levels 2. visceral fat and subcutaneous fat(measured by CT)
Cyganek Et al.[23]	2011	Poland	Liraglutide	Case report	1	18	14 weeks	1. HbA1c level 2. weight,fat issue amount 3. waist circumference.
Miller Et al.[24]	2014	U.S.	Metformin	Pilot, open-label study	31	11.18	3 months	1. Body fat (measured by dual-energy X-ray absorptiometry) 2. BMI SDS 3. appetite and satiety (using Hyperphagia Questionnaire)
Authors	Publication Year	Country of Study	Medication	Study Design	Case Number	Age Group	Length	Outcome Measure

Table 5. Chart of Clinical Trials for Diabetes and Obesity Drugs (Results).

Authors	Results								
	Height	BMI	Body fat	Appetite	HbA1c	Blood sugar	Lipid	ghrelin	Others
Salehi Et al.[19]	-	No change	No change	decreased	decreased	-	-	No change	-
Sze Et al.[20]	-	-	-	decreased	-	decreased	-	No change	1. lowered insulin, increased insulin secretion rate 2. decreased PYY and glucagon-like peptide-1 3. Unchanged energy expenditure
Fintini Et al.[21]	-	decreased	-	-	decreased	decreased	-	-	decreased waist circumference
Senda Et al.[22]	-	decreased	decreased	decreased	decreased	-	-	decreased	1. decreased Leptin 2. increased Insulin 3. Normal range of leptin and adiponectin level
Cyganek Et al.[23]	-	decreased	decreased	-	decreased	-	-	-	1. decreased waist circumference 2. slightly increased Fasting C-peptide and insulin levels
Miller Et al.[24]	-	decreased	-	decreased	-	-	-	-	Responders to metformin had higher 2-h glucose levels on OGTT and higher fasting insulin levels.
Kim Et al.[25]	-	dose-dependently decreased	decreased	decreased	-	-	decreased Triglycerides	-	Changes in Behavior were consistent with dose-dependent changes in the Total score

Studies of Medications for Diabetes and Obesity

One study on Beloranib, five studies on Liraglutide or Exenatide and one study on Metformin were included.[19-25] (**Table 4, 5**)

All of these studies focus on the effects of diabetes and obesity drugs on patients with PWS. After 4 weeks' Beloranib treatment in 17 adult patients, body weight, and body mass reduction were detected along with improved biochemical indexes including triglycerides, the decrease in BMI was dose-dependent.[25] As for the five studies focusing on GLP-1 receptor agonists, results showed that patients had decreased appetite and reduced BMI in three trials, decreased body fat and waist circumference in two trials, and mostly with reduced HbA1c level after treatments.[19-23] The Metformin study involved 31 patients with treatment of 3 months, showed reduced appetite and BMI, and blood sugar level.[24] None of seven trials included height as a measurement. No significant adverse effect was observed in these studies.

Intranasal Oxytocin (OXT)

As an emerging focus area for researchers, OXT has been considered a promising medication for PWS. Most characteristics of PWS result from the absence of expression of the paternally derived genes located on chromosome 15 at the locus q11·2-13, and one of the not expressed genes in this region is MAGEL2, whose deficiency might lead to a major reduction of OXT.[29] OXT has an important role in influencing the life quality of patients with PWS, such as feeding behaviors, social interactions, and emotional reactivity.[15] Most of our selected studies confirmed the improvement in behavior after OXT treatment. However, there was one study by Einfeld failed to show any impact.[17] We believe that this could be related to multiple factors. First, OXT works better in younger children. In the study of Kuppens et al, significant changes in behaviors after OXT treatment were only reported in the group of children under 11 years old, whereas subjects in Einfeld's study were all over 12 years old. Secondly, the delivery of OXT may also be a concern. In Einfeld's study, there was no plasma analysis, therefore it was hard to determine whether OXT was successfully delivered.

Although some results indicated increase in height and decrease in appetite with OXT treatment, the data is very limited this point. To validate OXT's effect on body mass and height, further studies with longer duration and bigger sample size are needed, set both body fat composition and lean body mass as well as BMI, metabolic profile as outcome measurements, in addition the efficacy of delivery and bioavailability of intranasal oxytocin will also need to be studied. Furthermore, the data of OXT effect on behaviors is far from enough, the future studies should focus on OXT treatment on social communication and behavioral profiles cross different age groups, and different severity or co-morbidity subgroups. We foresee extending clinical usage with more data collected.

Drugs for diabetes mellitus and obesity

As pointed out above, some drugs for diabetes mellitus also could potentially play an important role in the treatment of PWS.

Metformin is the first line treatment for Type 2 Diabetes Mellitus (T2DM), with the main effect to decrease liver glucose production. Researchers currently relate this medication to the treatment of patients with PWS since T2DM and PWS share a lot of similarities and connections. With its known weight loss capacity, we believe that Metformin has the potential to be an important part of treatment for PWS especially those associated glucose intolerance and insulin resistance. More studies with larger scale are needed to confirm the efficacy, the best time to initiate, with or without diabetes.

GLP-1 receptor agonists started to catch the attention as well. Multiple studies have been conducted to investigate the effectiveness of GLP-1 agonist treatment in patients with PWS, whose results supported the efficacy in different levels.[19-23] In view of its weight loss benefit and anti-diabetes effect, similar to metformin, there should be some value of this group of medications in the treatment of PWS, particularly those with glucose intolerance or diabetes. Further studies are necessary to investigate the long-term effects of GLP-1 receptor agonists on body mass and composition in PWS, as well as their adverse event profile. Their administration route as an injection might limit its use.

Apart from Diabetes medications, there is another noteworthy drug called Beloranib, an inhibitor of the enzyme METAP2, is a former drug candidate to treat obesity. It has approved efficacy in body weight loss and hyperphagia reduction, which are very important for PWS. Beloranib should have some potential to serve as a medication for patients with PWS, however this medication halted during phase III clinical trail due to unclear second deaths, further studies need to be conducted to assure the safety before it could move forward.

Other treatment perspectives

We discussed three major drug categories in PWS, there are other important aspects of treatments should be addressed here. First of all, early detection and intervention are paramount and currently still lag behind.[30,31] Prenatal screening methods including DNA methylation and high-resolution chromosomal SNP microarrays should be considered and newborn screening (NBS) could be applied basing on the utilization of next-generation sequencing and focusing on multiple PCR-based fragments from copy-number-determining chromosomal regions.[32] Early detection and early intervention lead a much better prognosis.

Secondly, caregivers play a very important role[33] in PWS treatment, however, most parents suffer from significant stress and require a great deal of counseling and training.[34] Their stress level and parenting style directly impact on the outcome. Haig and Woodcock investigated 10 caregivers of

patients with PWS through interviews and questionnaires, suggested the importance for caregivers to increase their flexibility and assure smooth transition.[35]

Third, behavioral intervention has been essential for PWS treatment. Patients with PWS share a lot in common in social-cognitive challenges with ASD patients, whose most empirically studied and validated treatment is behavioral treatment.[36] Dimitropoulos, Zyga, and Russ directly delivered a 6-week play-based intervention to eight children through telehealth[37] the participants completed the program without much difficulty and showed good acceptability to the behavioral intervention. Adolescents with PWS usually show aggressive reactions.[38] Soles of the Feet (SoF) is a mindfulness-based meditation technique developed by ONE Research Institute.[39] It kept away from the situations which cause anger and aggressive reactions. To evaluate the effectiveness of this meditation on patients with PWS, Singh, Lancioni, and Myers et al[40] found patients' physical aggression was almost completely resolved and verbal aggression significantly decreased after SoF, and these improvements were maintained after 12 months.

CONCLUSION AND FUTURE DIRECTIONS

This systematic review discussed the latest clinical trials for PWS and discussed the current treatment advancement. Of 1,139 potentially relevant articles from PubMed, MEDLINE, and Scopus from 2000 to 2017, we extracted 34 relevant articles with 20 clinical trials. As discussed above, in addition to the well-established therapy GH with further confirmed efficacy, the newer experimental OXT and diabetes and obesity drugs (Metformin, GLP-1 agonists, and Beloranib) have demonstrated certain positive effect on improving the symptoms of PWS which worth further investigations. Concomitant application among these drugs is also potentially important since they have divergent and complementary functions. Further studies particularly for these new emerging drugs, might also include GH too, are needed to look into their correlation with different PWS subtypes, such as those with different genetic or phenotypes, those co-existed with ASD, Depression, DM, GI disturbances, hypothyroidism or others, correlation of behavioral changes and hormonal parameters, the molecular mechanism of these therapies, and more specific target solutions. The future direction we believe should be, detect early and treat early with effective drug therapies in the combination of behavioral interventions for different subtypes, establish effective protocols, ultimately serve PWS population for better outcomes.

CONFLICT OF INTEREST
None

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