The Complexity of Care: A Comprehensive Look at Prader-Willi Syndrome from Symptoms to Emerging Therapies

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Disclosure

- Neither I, nor the planning committee/peer reviewer have any relevant financial relationships to disclose in relation to this activity.

Objectives

Review the pathophysiology, presentation, and diagnostic approach of Prader-Willi Syndrome

Discuss the current nutritional, behavioral and pharmacological approaches to the management of Prader-Willi Syndrome

Describe emerging therapies for Prader-Willi Syndrome

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Living with Prader-Willi Syndrome

https://youtu.be/FYnfhYIdKog?si=HvfdjymfDClOiSaG

Prader-Willi Syndrome (PWS)

- PWS is a genetic multisystem disorder resulting from certain gene abnormalities in chromosome 15
- It is caused by errors, most often spontaneous, in genomic imprinting
- It is the most common genetic cause of life-threatening childhood obesity
- Every patient is unique – symptoms and severity of PWS are variable

- Mahmoud R, Kimonis V, Butler MG. Clinical Trials in Prader-Willi Syndrome: A Review. *Int J Mol Sci*. 2023;24(3):2150. Published 2023 Jan 21. doi:10.3390/ijms24032150

Epidemiology

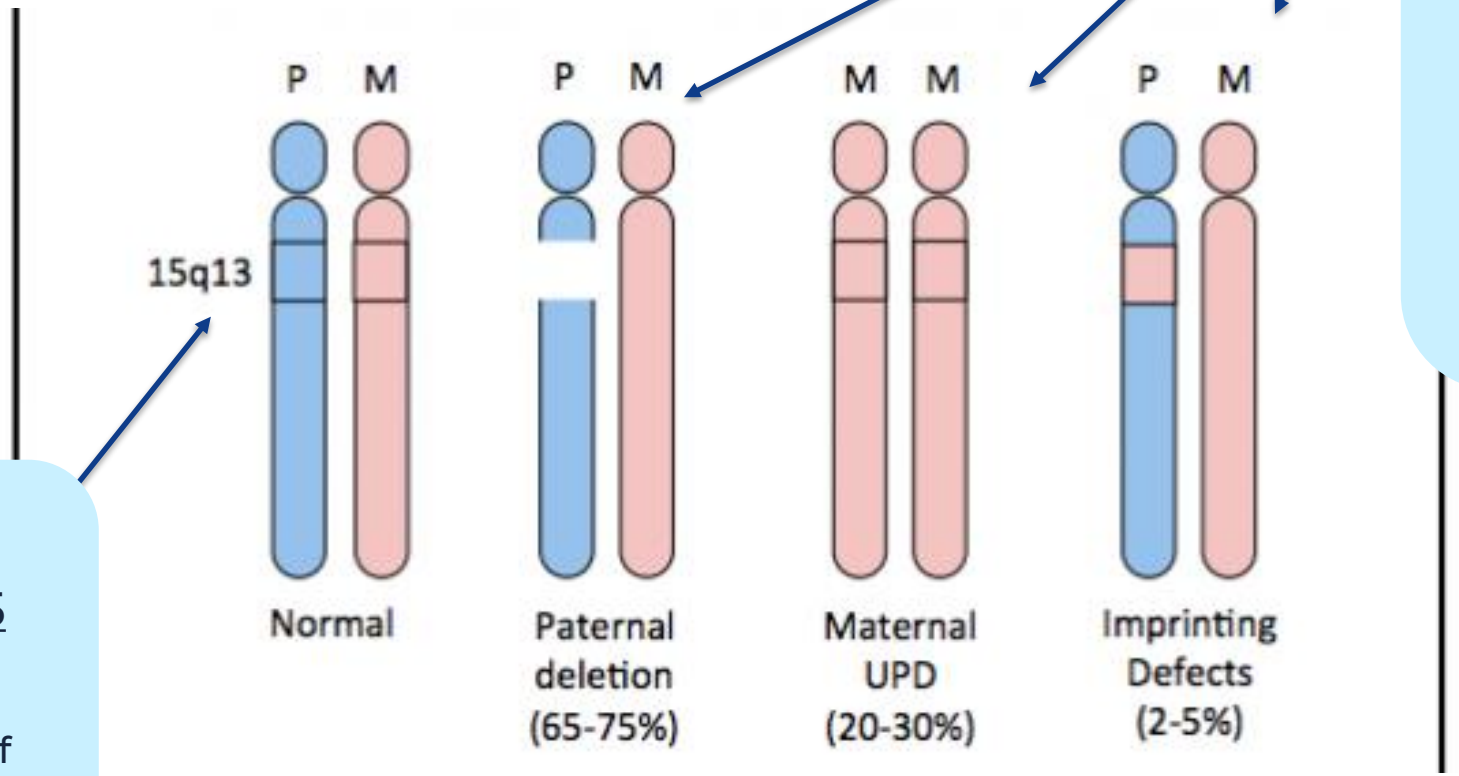
Incidence of PWS is estimated to be between 1 in every 10,000 to 1 in every 30,000 births

PWS affects about 350,000 to 400,000 individuals worldwide

Males and females are equally affected by PWS

- Bohonowych J, Miller J, McCandless SE, Strong TV. The Global Prader-Willi Syndrome Registry: Development, Launch, and Early Demographics. *Genes (Basel)*. 2019;10(9):713. Published 2019 Sep 14. doi:10.3390/genes10090713
- Butler MG. Prader-Willi Syndrome: Obesity due to Genomic Imprinting. *Curr Genomics*. 2011;12(3):204-215. doi:10.2174/138920211795677877

Genetic Subtypes of PWS



Chromosome 15 in PWS

Paternal region of 15q11-q13 is missing in each genetic type

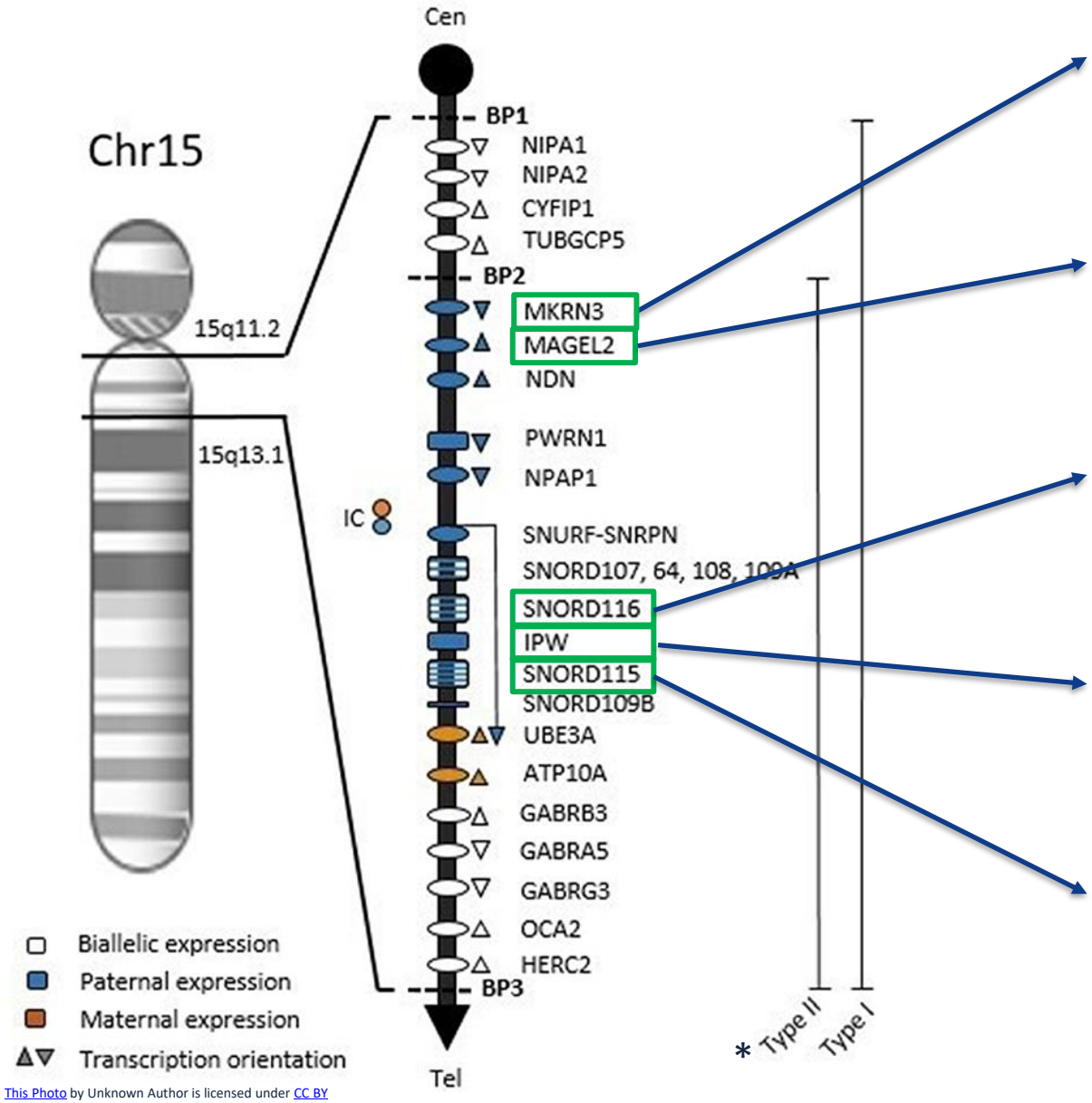
3 Genetic Subtypes:

- Paternal Deletion
- Maternal uniparental disomy
- Imprinting defect

Normal Chromosome 15

Maternal (M) and paternal (P) region of 15q11-q13 present

- IPWSO. IPWSO Summit Meetings: Dan Driscoll "Overview of NBS & Brief Discussion of PWS". YouTube. May 23, 2023. Accessed December 3, 2025. https://youtu.be/dlKNKJX8BGQ?si=NcnmYNb2eg4QwAtf.
- Mahmoud R, Kimonis V, Butler MG. Clinical Trials in Prader-Willi Syndrome: A Review. Int J Mol Sci. 2023;24(3):2150. Published 2023 Jan 21. doi:10.3390/ijms24032150



MKRN3

Mutations may lead to premature adrenarche

MAGEL2

Neonatal hypotonia, feeding difficulty, social/learning difficulties; Also involved in Schaaf-Yang syndrome

SNORD116

Part of the minimal critical region for PWS; Thought to drive the whole PWS phenotype; involved in hyperphagia

IPW

Part of the minimal critical region for PWS

SNORD115

Involved in serotonin 5HT2c receptor modulation, and may impact MC4R signaling

*Type I and Type II designations are two different deletion sizes. Type I typically gives way to a more severe presentation of symptoms

- Abreu AP, Toro CA, Song YB, et al. MKRN3 inhibits the reproductive axis through actions in kisspeptin-expressing neurons. *J Clin Invest*. 2020;130(8):4486-4500. doi:10.1172/JCI136564
- Abuzzahab MJ, Dubern B, Goldstone AP, et al. Improving the diagnosis of hyperphagia in melanocortin-4 receptor pathway diseases. *Obesity (Silver Spring)*. 2025;33(7):1217-1231. doi:10.1002/oby.24287
- Fountain MD, Schaaf CP. Prader-Willi Syndrome and Schaaf-Yang Syndrome: Neurodevelopmental Diseases Intersecting at the *MAGEL2* Gene. *Diseases*. 2016;4(1):2. Published 2016 Jan 13. doi:10.3390/diseases4010002
- Salles J, Lacassagne E, Eddiry S, Franchitto N, Salles JP, Tauber M. What can we learn from PWS and SNORD116 genes about the pathophysiology of addictive disorders?. *Mol Psychiatry*. 2021;26(1):51-59. doi:10.1038/s41380-020-00917-x
- Tauber M, Hoybye C. Endocrine disorders in Prader-Willi syndrome: a model to understand and treat hypothalamic dysfunction. *Lancet Diabetes Endocrinol*. 2021;9(4):235-246. doi:10.1016/S2213-8587(21)00002-4

Growing with PWS

Infancy:

- Hypotonia
- Difficulty feeding
- Genital hypoplasia
- Higher body fat content
- Growth hormone deficiency

Childhood:

- Increased interest in food & weight gain
- Developmental delays
- Behavioral problems
- Intellectual disabilities
- Premature adrenarche

Adolescence:

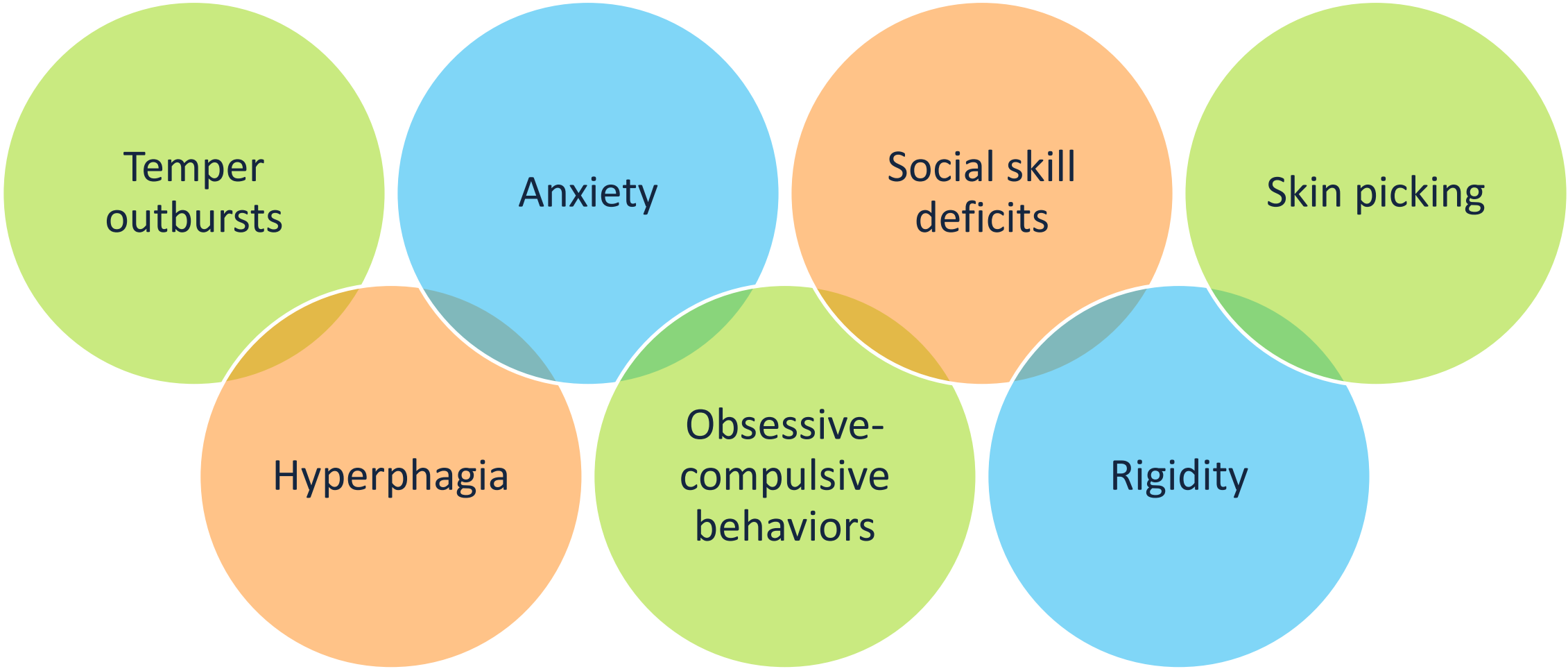
- Hyperphagia
- Intellectual disabilities & behavioral problems
- Social skill deficits
- Hypogonadism & delayed puberty

Adulthood:

- Continuation of the earlier stages
- Hyperphagia may lessen, giving the individual the ability to feel full
- Infertility

- Bohonowych J, Miller J, McCandless SE, Strong TV. The Global Prader-Willi Syndrome Registry: Development, Launch, and Early Demographics. Genes (Basel). 2019;10(9):713. Published 2019 Sep 14. doi:10.3390/genes10090713
- Butler MG. Prader-Willi Syndrome: Obesity due to Genomic Imprinting. Curr Genomics. 2011;12(3):204-215. doi:10.2174/138920211795677877
- Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi Syndrome. 1998 Oct 6 [Updated 2024 Dec 5]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1330/
- Höybye C, Tauber M. Approach to the Patient With Prader-Willi Syndrome. *J Clin Endocrinol Metab*. 2022;107(6):1698-1705. doi:10.1210/clinem/dgac082
- Shawn E. McCandless, The Committee on Genetics; Health Supervision for Children With Prader-Willi Syndrome. *Pediatrics* January 2011; 127 (1): 195–204. 10.1542/peds.2010-2820

Behavioral Aspects of PWS



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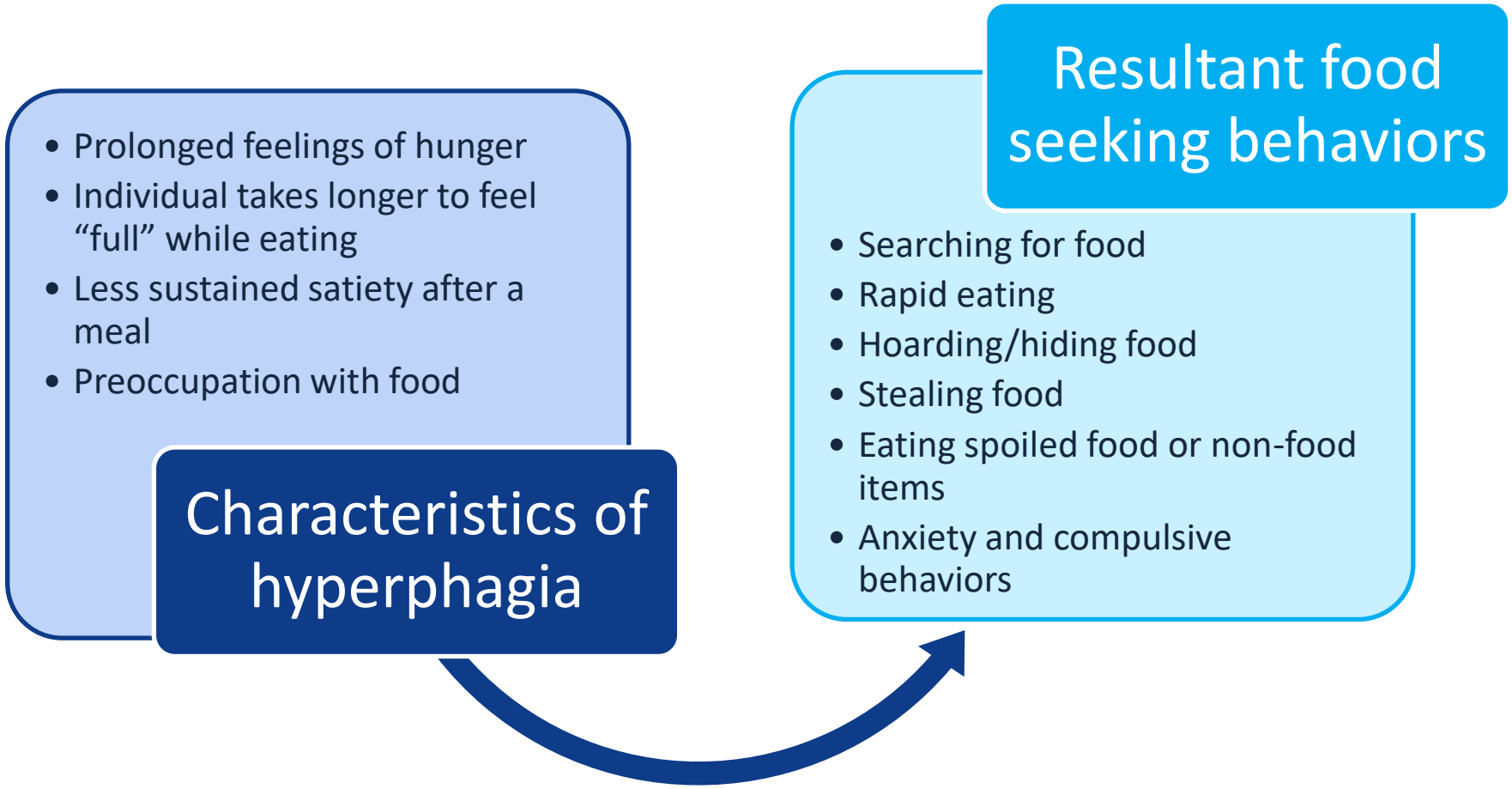
Hyperphagia

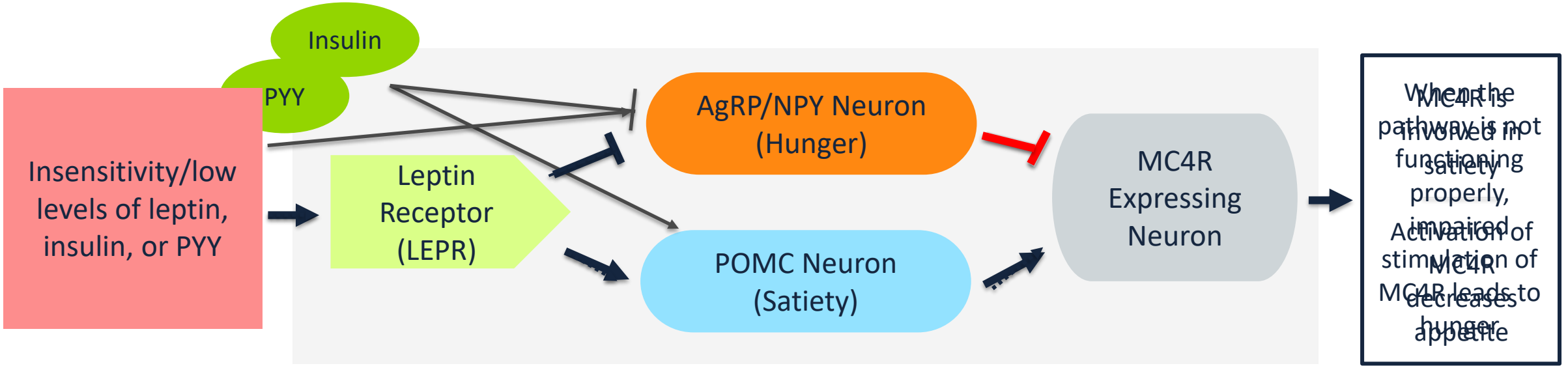
- Defined as a pathologic, insatiable hunger accompanied by abnormal food-seeking behaviors



• Heymsfield SB, Clément K, Dubern B, et al. Defining Hyperphagia for Improved Diagnosis and Management of MC4R Pathway-Associated Disease: A Roundtable Summary. *Curr Obes Rep*. 2025;14(1):13. Published 2025 Jan 25. doi:10.1007/s13679-024-00601-z

Pathophysiology of Hyperphagia

- PWS is a syndromic MC4R pathway disease
- When the MC4R pathway is not functioning properly, insensitivity to low levels of leptin, insulin, and PYY leads to signals of lack of satiety and POMC stimulation, resulting in hunger



Leptin-Melanocortin Pathway

Key:
- AgRP = Agouti-related peptide
- NPY = Neuropeptide Y
- POMC = Pro-opiomelanocortin
- MC4R = Melanocortin 4 Receptor

- Abuzzahab MJ, Dubern B, Goldstone AP, et al. Improving the diagnosis of hyperphagia in melanocortin-4 receptor pathway diseases. *Obesity (Silver Spring)*. 2025;33(7):1217-1231. doi:10.1002/oby.24287
- Miller JL, Gevers E, Bridges N, 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):1676-1685. doi:10.1210/clinem/dgad014
- Rahman QFA, Jufri NF, Hamid A. Hyperphagia in Prader-Willi syndrome with obesity: From development to pharmacological treatment. *Intractable Rare Dis Res*. 2023;12(1):5-12. doi:10.5582/irdr.2022.01127
- Wevrick R. Disentangling ingestive behavior-related phenotypes in Prader-Willi syndrome: Integrating information from nonclinical studies and clinical trials to better understand the pathophysiology of hyperphagia and obesity. *Physiol Behav*. 2020;219:112864. doi:10.1016/j.physbeh.2020.112864
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Pathophysiology of Hyperphagia

Deviations from proper functioning in PWS:

- Hypothalamic dysfunction
- Insensitivity to leptin
- Low levels of insulin and peptide YY

Other contributing factors:

- Higher activity in the reward/limbic regions
- Dysfunction of oxytocin neurons
- Potential role of ghrelin

- Abuzzahab MJ, Dubern B, Goldstone AP, et al. Improving the diagnosis of hyperphagia in melanocortin-4 receptor pathway diseases. *Obesity (Silver Spring)*. 2025;33(7):1217-1231. doi:10.1002/oby.24287
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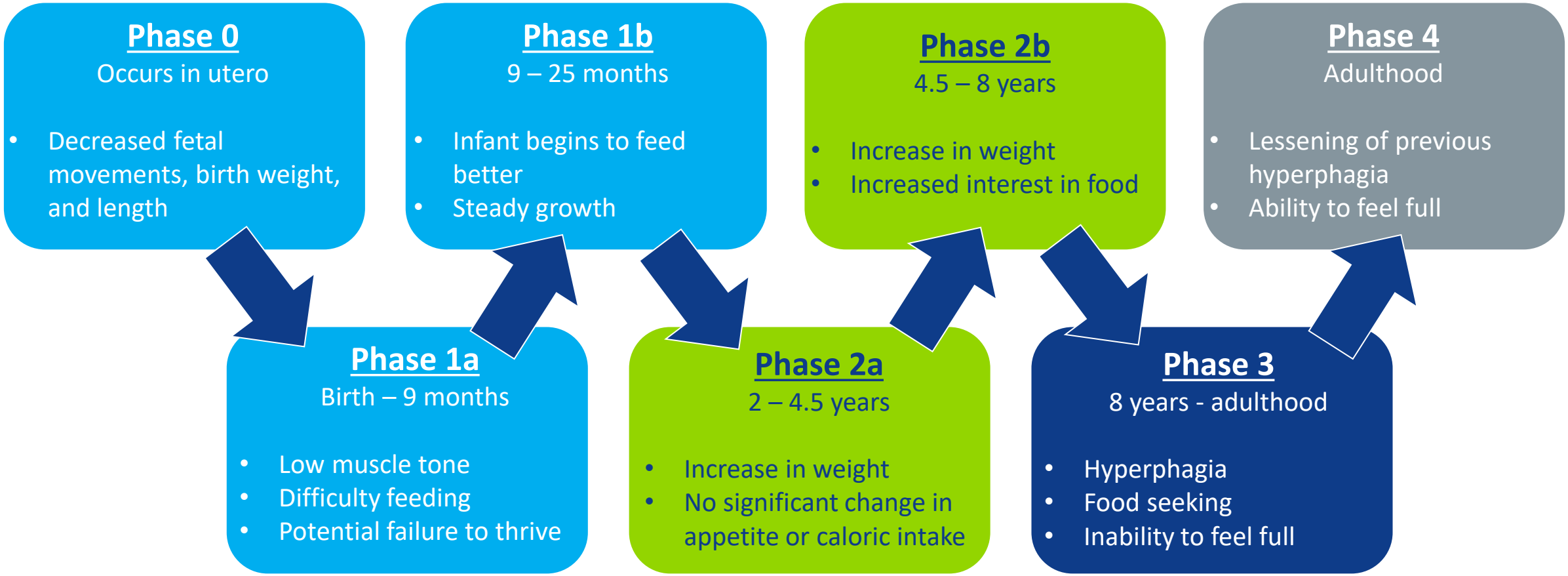
- Xu B, Goulding EH, Zang K, et al. Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. *Nat Neurosci*. 2003;6(7):736-742. doi:10.1038/nn1073

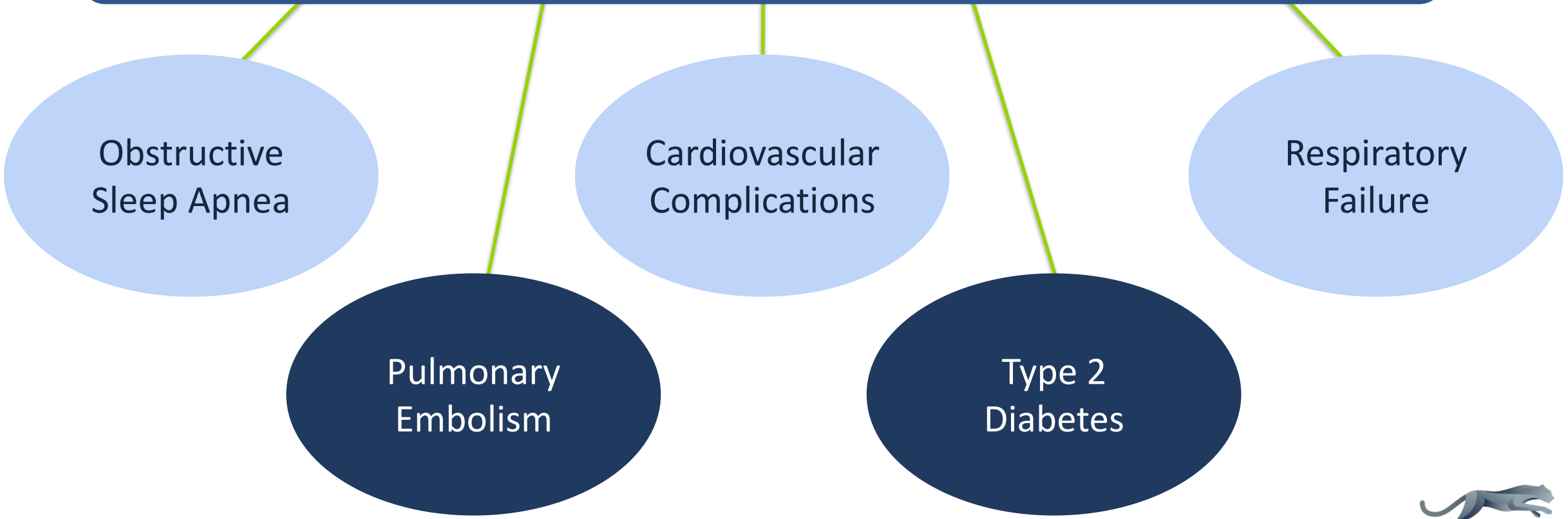
Nutritional Phases



- Miller JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader-Willi syndrome. *Am J Med Genet A*. 2011;155A(5):1040-1049. doi:10.1002/ajmg.a.33951

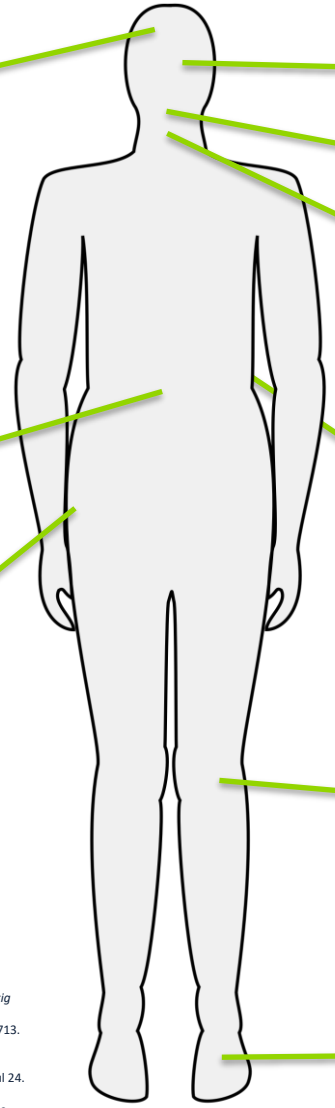
Consequences of Hyperphagia/Obesity

Obesity and obesity-related complications are a common cause of morbidity and mortality in PWS



• 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(1):104379. doi:10.1016/j.ejmg.2021.104379

Other Features/Comorbidities of PWS



- Temperature dysregulation
- Sleep/wake disturbances
- High pain threshold
- Visual abnormalities (myopia, strabismus)
- Inability to vomit
- Reduced salivation
- Hypothyroidism
- Gastrointestinal complications
- Scoliosis
- Delayed hip development (possible dysplasia)
- Osteoporosis
- Hypotonic pes plantus (flat feet)

- Bantim YCV, Kussaba ST, de Carvalho GP, Garcia-Junior IR, Roman-Torres CVG. Oral health in patients with Prader-Willi syndrome: current perspectives. *Clin Cosmet Investig Dent*. 2019;11:163-170. Published 2019 Jul 4. doi:10.2147/CCIDE.S183981
- Bohonowych J, Miller J, McCandless SE, Strong TV. The Global Prader-Willi Syndrome Registry: Development, Launch, and Early Demographics. Genes (Basel). 2019;10(9):713. Published 2019 Sep 14. doi:10.3390/genes10090713
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- Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi Syndrome. 1998 Oct 6 [Updated 2024 Dec 5]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1330/
- Miao M, Zhao GQ, Zhou Q, Chao YQ, Zou CC. Orthopedic manifestations in children with Prader-Willi syndrome. *BMC Pediatr*. 2024;24(1):118. Published 2024 Feb 14. doi:10.1186/s12887-024-04603-7

Morbidity and Mortality

Statistics from “The burden of illness in Prader-Willi Syndrome: a systematic literature review”

- Estimates show individuals with PWS have a higher mortality rate and a greater relative risk of mortality
- Respiratory failure was found to be the most common single cause of death across all age groups
  - Accounted for 31.4% of deaths in a large US retrospective cohort study (n=486)
  - Accounted for 40.4% of deaths in a French retrospective, observational cohort study (n=104)
- Hyperphagia related morbidity and mortality
  - Causes of death include high rates of accidents, choking, GI perforation, GI distension, GI obstruction
  - In the US retrospective cohort study, the above causes of death attributed to about 1/3 of all deaths and half of deaths in patients < 18 years of age
- The results of this systematic review found that individuals with PWS have a reduced life expectancy compared to the general population

- Dempsey D, Hall M, Lanning B, et al. The burden of illness in Prader-Willi syndrome: a systematic literature review. *Orphanet J Rare Dis*. 2025;20(1):374. Published 2025 Jul 24. doi:10.1186/s13023-025-03787-0

Diagnostic Criteria

Major Criteria	Minor Criteria
• Neonatal and infantile central hypotonia • Difficulty sucking • Feeding difficulties requiring special assistance, poor weight gain/failure to thrive • Rapid or excessive weight gain on weight-for-length chart between 1 and 6 years of age • Hyperphagia • Characteristic facial features • Hypogonadism • Global developmental delay, learning problems	• Decreased movement or infantile lethargy • Characteristic behavioral problems • Sleep disturbances or sleep apnea • Short stature for genetic background, noticeable by age 15 • Hypopigmentation • Small hands and feet for height and age standards • Narrow hands with straight ulnar border • Eye abnormalities • Thick, viscous saliva • Speech articulation defects • Skin picking

confirms the diagnosis

- Holm VA, Cassidy SB, Butler MG, et al. Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics. 1993;91(2):398-402.

Diagnosis & Genetic Testing

DNA Methylation Analysis

Detects > 99% of PWS cases

Chromosomal Microarray (Olgio SNP Array)

Identifies the deletion class and size

- Butler MG. Benefits and limitations of prenatal screening for Prader-Willi syndrome. Prenat Diagn. 2017;37(1):81-94. doi:10.1002/pd.4914
- IPWSO. IPWSO Summit Meetings: Dan Driscoll "Overview of NBS & Brief Discussion of PWS". YouTube. May 23, 2023. Accessed December 3, 2025. https://youtu.be/dlKNKJX8BGQ?si=NcnmYNb2eg4QwAtf.

KNOWLEDGE CHECK 1

Which of the following is a characteristic of PWS?

A) Low hunger drive in adolescence

B) Developmental delays

C) Early achievement of developmental milestones

D) Higher than average muscle tone

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KNOWLEDGE CHECK 2

Patient MP just received her DNA methylation analysis results. The results were positive for PWS.

What would be an appropriate next step?

A) No further testing is needed, this test can detect Patient MP's genetic subtype.

B) This is a highly inaccurate test. It should be repeated to rule out a false positive result.

C) A Chromosomal Microarray should be performed to determine Patient MP's genetic subtype.

D) DNA Methylation Analysis was performed in error as this is not an appropriate test for PWS.

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Objectives

Review the pathophysiology, presentation, and diagnostic approach of Prader-Willi Syndrome

Discuss the current nutritional, behavioral and pharmacological approaches to the management of Prader-Willi Syndrome

Describe emerging therapies for Prader-Willi Syndrome

Nutritional Management

Infancy to ~15 months

- Typically require assisted feeding
  - NG/OG feeds if oral feeds are not tolerated or special nipples if oral feeds are tolerated
- Breast milk fortification or concentrated formula
- Weigh the infant regularly

As the individual's weight begins to increase, caloric intake must be decreased

~15 - 18 months to adulthood

- Caloric needs are typically 60-80% of the recommended daily allowance for age
- Importance of physical activity
- Various dietary recommendations exist, but there is no agreed upon diet
- Vitamin and mineral supplementation is necessary for calorie restricted diets

- Borgie KH. Nutritional Guidelines: Adolescence through Adulthood for Persons with Prader-Willi Syndrome. Prader-Willi Syndrome Association. 1995. Accessed December 27, 2025.
- Miller JL, Tan M. Dietary Management for Adolescents with Prader-Willi Syndrome. Adolesc Health Med Ther. 2020;11:113-118. Published 2020 Aug 25. doi:10.2147/AHMT.S214893
- Shawn E. McCandless, The Committee on Genetics; Health Supervision for Children With Prader-Willi Syndrome. *Pediatrics* January 2011; 127 (1): 195–204. 10.1542/peds.2010-2820

Behavioral Management

Consistent routines, clear rules, and clear boundaries

- Create and post schedules daily; clearly communicate any changes in advance
- Keep rules consistent and do not give in
- Avoid ambiguity; offer preferential, limited choices

Positive reinforcement

- Encouraging positive behaviors when they occur will make the individual more likely to repeat these behaviors

Calm environment

- Create a safe space with sensory items; keep lighting soft; limit auditory stimuli

Limit access to food

- Identify and proactively manage opportunities for outside access to food (school, work, etc.)
- Avoid leaving food out; keep cabinets and fridges locked

Respond to tantrums with empathy, not a change of rules

- Use compassion and empathy to show the individual that their feelings are recognized, but do not give in to the behavior as this will lead to future tantrums

- Borgie KH. Nutritional Guidelines: Adolescence through Adulthood for Persons with Prader-Willi Syndrome. Prader-Willi Syndrome Association. 1995. Accessed December 27, 2025.
- Tula K. Guidelines for Behavior Management. Prader-Willi Syndrome Association. November 2022. Accessed December 27, 2025.

Pharmacologic Management

Recombinant Human Growth Hormone (rhGH)

Human Chorionic Gonadotropin (hCG)

Diazoxide Choline Continuous Release (DCCR)

Recombinant Human Growth Hormone (rhGH)

Benefits:

- Infants & children → Improved linear growth (height and weight), improved lean mass, improved motor development (strength and agility), possible improvement in attention and cognitive development
- Adults → bone strengthening, normalization of body composition

Use in PWS:

- Historically, approval of these agents was for the indication of growth hormone deficiency
  - Led to access difficulties for many children with PWS
- From AAP: Clinical experience suggest **treatment can begin as early as 2-3 months of age**
- From the Endocrine Society: After genetic confirmation of the diagnosis of PWS, rhGH treatment **should be considered and, if initiated, continued for as long as the demonstrated benefits outweigh the risks**

Deal CL, Tony M, Höybye C, et al. Growth Hormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2013;98(6):E1072-E1087. doi:10.1210/jc.2012-3888. Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome – PMC

Shawn E. McCandless, The Committee on Genetics; Health Supervision for Children With Prader-Willi Syndrome. *Pediatrics* January 2011; 127 (1): 195–204. 10.1542/peds.2010-2820

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Recombinant Human Growth Hormone (rhGH)

Monitoring/Screening Recommendations:

- Must perform sleep oximetry, preferably by polysomnographic (PSG) evaluation prior to treatment
- Additional recommendations prior to treatment initiation:
  - Endocrine examination
    - Bone age determination
    - Evaluation of hypothyroidism
    - IGF-I levels; GH response to provocative testing (adults)
    - Metabolic status evaluation (if 12 years or older or obesity present)
    - Evaluate cardiovascular risk and assess for hepatic steatosis (if obesity present)
    - Body composition evaluation
    - Consider adrenal evaluation
  - Assess developmental function, motor function, and cognitive status
  - Scoliosis evaluation
  - Must discuss risk vs benefit of treatment with caregivers

Deal CL, Tony M, Höybye C, et al. GrowthHormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2013;98(6):E1072-E1087. doi:10.1210/jc.2012-3888. Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome - PMC
Shawn E. McCandless, The Committee on Genetics; Health Supervision for Children With Prader-Willi Syndrome. *Pediatrics* January 2011; 127 (1): 195–204. 10.1542/peds.2010-2820

Recombinant Human Growth Hormone (rhGH)

rhGH Agent:

- Somatropin Recombinant carries an approval specifically for PWS
- Mechanism of Action: Therapeutically equivalent to human growth hormone of pituitary origin
- Formulation: Subcutaneous Injection
- Dosing: 0.24 mg/kg/week
- Contraindications: acute critical illness, active malignancy, hypersensitivity to somatropin or excipients, active proliferative or severe non-proliferative diabetic retinopathy, children with closed epiphyses, and children with PWS who are severely obese, have OSA, or have severe respiratory impairment

- Genotropin (somatropin). Package insert. Pharmacia & Upjohn Company LLC; 2025. Accessed January 7, 2026.
- Norditropin (somatropin). Package insert. Novo Nordisk Inc; 2025. Accessed January 7, 2026.
- Omnitrope (somatropin) Package insert. Sandoz Inc; 2025. Accessed January 7, 2026.

Recombinant Human Growth Hormone (rhGH)

Warnings, Precautions, & Adverse Events:

- Warnings/Precautions: Increased mortality with acute critical illness, sudden death in pediatric patients with PWS, neoplasms, impaired glucose tolerance and diabetes mellitus, intracranial hypertension, hypersensitivity, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphyses, progression of preexisting scoliosis, laboratory tests, lipoatrophy, pancreatitis, benzyl alcohol

- Adverse Reactions from Clinical Trials in PWS:
  - Edema, aggressiveness, arthralgia, benign intracranial hypertension, hair loss, headache, and myalgia

- Genotropin (somatropin). Package insert. Pharmacia & Upjohn Company LLC; 2025. Accessed January 7, 2026.
- Norditropin (somatropin). Package insert. Novo Nordisk Inc; 2025. Accessed January 7, 2026.
- Omnitrope (somatropin) Package insert. Sandoz Inc; 2025. Accessed January 7, 2026.

Human Chorionic Gonadotropin (hCG)

Use in PWS:

- Indicated for the treatment of undescended testes in males
  - A trial of this agent is recommended prior to surgery
  - Despite treatment, surgery may still be required (prior to age 3)

Benefits:

- Best to avoid general anesthesia use in this population due to low muscle tone in infancy and potential for underlying respiratory compromise
- Increased scrotal size
- Partial normalization of phallus length
  - Even if surgery is still necessary after medication trial, the above benefits improve surgical outcomes

- Bohonowych J, Miller J, McCandless SE, Strong TV. The Global Prader-Willi Syndrome Registry: Development, Launch, and Early Demographics. Genes (Basel). 2019;10(9):713. Published 2019 Sep 14. doi:10.3390/genes10090713
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- Shawn E. McCandless, The Committee on Genetics; Health Supervision for Children With Prader-Willi Syndrome. *Pediatrics* January 2011; 127 (1): 195–204. 10.1542/peds.2010-2820

Human Chorionic Gonadotropin (hCG)

Dosing & Administration:

- Formulation: Intramuscular injection
- Mechanism of Action: Stimulates the production of gonadal steroid hormones by stimulating the testes to produce androgens
- Dosing: Multiple dosing options for prepubertal cryptorchidism
  - 4000 units 3 times weekly x 3 weeks
  - 5000 units every second day x 4 injections
  - 500 units 3 times weekly x 4-6 weeks (may repeat course one month later using 1000 units/dose if unsuccessful)
  - 15 injections of 500 to 1000 units administered over 6 weeks

- Novarel (Chorionic Gonadotropin for Injection). Package Insert. Ferring Pharmaceuticals Inc. Accessed January 26, 2026.
- Pregnyl (Chorionic Gonadotropin for Injection). Package Insert. Organon USA Inc; 2006. Accessed January 26, 2026.

Human Chorionic Gonadotropin (hCG)

Warnings, Precautions, & Adverse Events:

- Contraindications: Precocious puberty, prostatic carcinoma or other androgen-dependent neoplasm, and prior allergic reaction to HCG
- Warning/Precautions: Anaphylaxis, fatal "Gasping Syndrome" in premature infants (due to benzyl alcohol), thromboembolism, and caution with certain comorbid conditions due to potential fluid retention
- Adverse Effects: Headache, irritability, restlessness, depression, fatigue, edema, precocious puberty, gynecomastia, injections site pain, and hypersensitivity reactions

- Novarel (Chorionic Gonadotropin for Injection). Package Insert. Ferring Pharmaceuticals Inc. Accessed January 26, 2026.
- Pregnyl (Chorionic Gonadotropin for Injection). Package Insert. Organon USA Inc; 2006. Accessed January 26, 2026.

Diazoxide Choline Continuous Release (DCCR)

Use in PWS:

- Treatment of hyperphagia in adults and pediatric patients 4 years of age and older with PWS

Clinical Studies/Benefits:

- Studied in a 13-week, randomized, double-blind placebo-controlled phase 3 trial, followed by an open-label extension and a randomized withdrawal study
  - Primary outcome: hyperphagia change from baseline measured using the Hyperphagia Questionnaire for Clinical Trials (HQ-CT)
  - Open-label extension: statistically significant improvement at weeks 13, 26, 39, and 52 weeks
  - Randomized withdrawal: statistically significant worsening of HQ-CT scores by week 12 in the placebo arm
  - Exploratory endpoints: Improvements seen in disease severity and behavioral measures

- Miller JL, Bridges N, Felner EI, et al. Diazoxide Choline Extended-Release Tablets in Prader-Willi Syndrome: A Randomized, Double-Blind, Withdrawal Period Study. *J Clin Endocrinol Metab*. Published online January 2, 2026. doi:10.1210/clinem/dgaf661
- Miller JL, Gevers E, Bridges N, 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):1676-1685. doi:10.1210/clinem/dgad014
- Miller JL, Gevers E, Bridges N, 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(2):252-261. doi:10.1002/oby.23928

Diazoxide Choline Continuous Release (DCCR)

- Formulation: Orally administered extended-release tablet
- Mechanism of Action: Exact mechanism unknown; diazoxide is a potent activator of the adenosine triphosphate-sensitive potassium channel
- Dosing:

Weight	Recommended Once Daily Dosage			
	Starting Dosage	Titration Dosage	Titration Dosage	Target Maintenance Dosage
	Weeks 1 and 2	Weeks 3 and 4	Weeks 5 and 6	
20 kg to <30 kg	25 mg	50 mg	75 mg	100 mg
30 kg to <40 kg	75 mg	150 mg	150 mg	150 mg
40 kg to <65 kg	75 mg	150 mg	225 mg	225 mg
65 kg to <100 kg	150 mg	225 mg	300 mg	375 mg
100 kg to <135 kg	150 mg	300 mg	375 mg	450 mg
≥135 kg	150 mg	300 mg	450 mg	525 mg

- Contraindications: Known hypersensitivity to diazoxide, other components of DCCR or thiazides
- Warnings & Precautions: Hyperglycemia, fluid overload
- Adverse Reactions: Hypertrichosis, edema, hyperglycemia, rash, pyrexia, arthralgia, influenza, nasopharyngitis
- Monitoring Parameters: fasting glucose, HbA1c, signs/symptoms of edema or fluid overload

• Vykat XR (diazoxide choline). Package insert. Soleno Therapeutics, Inc; 2025. Accessed January 7, 2026.

Other General Management Practices

Sleep Disorders

- Annual evaluation for sleep disorders
- Central Sleep Apnea
  - PSG in infancy at time of PWS diagnosis to rule out central sleep apnea (CSA)
  - Supplemental oxygen
  - Positive airway pressure
- Obstructive Sleep Apnea (OSA)
  - Continuous positive airway pressure (CPAP)
  - CPAP adherence may be troublesome
- Narcolepsy → treat per practice parameters
- Excessive Daytime Sleepiness → same guidance from case reports
- Insomnia → trial of melatonin

- Bohonowych J, Miller J, McCandless SE, Strong TV. The Global Prader-Willi Syndrome Registry: Development, Launch, and Early Demographics. *Genes (Basel)*. 2019;10(9):715. Published 2019 Sep 19. doi:10.3390/genes10090715
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Orthopedic Management

- Scoliosis
  - Screening radiographs should be started once the patient can sit independently
  - Continue annually until age 4
  - Trunk strengthening
  - Delay unsupported upright sitting until the child can spontaneously pull themselves to a sitting position
  - Spinal CAT/TAP
  - Bracing
  - Spinal surgery
- Delayed ambulation and hypotonia
  - Ankle-Foot Orthoses; Physical Therapy
- Delayed hip development/hip dysplasia
  - Activity and weight-bearing exercise
- Osteoporosis or osteopenia
  - Lifelong monitoring; Supplementation

Other General Management Practices

Vision & Dental

- Individuals with PWS have reduced salivation → increased risk for dental caries
  - Dental inspection/cleaning is recommended twice yearly
- High prevalence of vision abnormalities → annual or bi-annual ophthalmic evaluation
  - Strabismus surgery

Hypothyroidism

- Central (secondary) hypothyroidism may be more common in the PWS population
- Growth hormone treatment has the potential to uncover or worsen hypothyroidism
- Pharmacologic agent = Levothyroxine

Other

- Monitoring and treatment of other obesity related comorbid conditions per guidelines
- Caution when treating infections/general illness
- Central adrenal insufficiency screening

- Alsaffar H, Abdullah WH, Hussein SA. Hypothyroidism in Paediatric Patients with Prader-Willi Syndrome; Regular Monitoring is Recommended. *Medical Journal of Babylon* 19(2):p 123-125, Apr–Jun 2022. doi:10.4103/MJBL.MJBL_43_22
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KNOWLEDGE CHECK 3

What is the name of the FDA approved agent for treating hyperphagia in PWS?

A) Somatropin Recombinant

B) Diazoxide Choline Continuous Release

C) Human Chorionic Gonadotropin

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KNOWLEDGE CHECK 4

Patient JV was recently prescribed Somatropin Recombinant Growth Hormone.

Which of the following is a benefit of JV's new treatment?

- A) Normalization of body composition
- B) Appetite regulation
- C) Improved sleep patterns in obstructive sleep apnea
- D) Normalization of thyroid levels

KNOWLEDGE CHECK 4

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Which of the following is a benefit of JV's new treatment?

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- D) Normalization of thyroid levels

Objectives

Review the pathophysiology, presentation, and diagnostic approach of Prader-Willi Syndrome

Discuss the current nutritional, behavioral and pharmacological approaches to the management of Prader-Willi Syndrome

Describe emerging therapies for Prader-Willi Syndrome

Agents in Phase 1 and 2 Clinical Trials

Phase 1:

RM-718

- Mechanism: MC4R agonist
- Use(s): **Hyperphagia**; Obesity

EPM301

- Mechanism: Cannabidiol acid methyl ester
- Use(s): **Hyperphagia**; Anxiety; Sleep disturbances

Phase 2:

BMB-101

- Mechanism: 5-HT2C agonist
- Use(s): **Hyperphagia**; Neurobehavioral challenges; Weight loss

Setmelanotide

- Mechanism: MC4R agonist
- Use(s): **Hyperphagia**; Obesity

TNX-2900

- Mechanism: Intranasal oxytocin
- Use(s): **Hyperphagia**; Neurobehavioral challenges

CSTI-500

- Mechanism: Triple monoamine reuptake inhibitor
- Use(s): **Hyperphagia**; Neurobehavioral challenges

- Bright Minds Biosciences Pty Ltd. A 2-Part Study to Assess Efficacy, Safety and Tolerability of BMB-101 for the Treatment of Patients With Prader-Willi Syndrome. ClinicalTrials.gov identifier: NCT07266324. December 5, 2025. Accessed January 15, 2026. https://clinicaltrials.gov/study/NCT07266324#collaborators-and-investigators
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Agents in Phase 3/Pivotal Clinical Trials

Pitolisant

- Proposed Indication: **Excessive daytime sleepiness (EDS)**
- Mechanism of action: Histamine-3 receptor (H3R) antagonist/inverse agonist
- Population: Patients ≥ 6 years of age with PWS
- Primary Outcome: Patient-reported outcome measure of change in severity of EDS
- Other Outcomes: Irritable and disruptive behaviors, hyperphagia, additional behavioral endpoints

ARD-101

- Proposed Indication: **Hyperphagia**
- Mechanism of action: Bitter taste receptor (TAS2R) agonist
- Population: Patients ≥ 10 years of age with PWS
- Primary Outcome: Change in HQ-CT score from baseline to week 12
- Other Outcomes: Clinical and caregiver global impression of severity scores for hyperphagia

PBF-999

- Proposed Indication: **Hyperphagia**
- Mechanism of action: Novel dual phosphodiesterase 10 and adenosine A2a inhibitor
- Population: Patients ≥ 12 years to 65 years of age with PWS (per phase 2 protocol)
- Study Outcomes: Not yet specified (HQ-CT and Caregiver Global Impression of Change used in Phase 2)

- Aardvark Therapeutics, Inc. ARD-101 for Treatment of PWS: The Hunger Elimination or Reduction Objective Trial (HERO). ClinicalTrials.gov identifier: NCT06828861. January 8, 2026. Accessed January 15, 2026. https://clinicaltrials.gov/study/NCT06828861
- Harmony Biosciences Management, Inc. A Study of Pitolisant in Patients With Prader-Willi Syndrome. ClinicalTrials.gov identifier: NCT06366464. December 3, 2025. Accessed January 15, 2026. https://clinicaltrials.gov/study/NCT06366464
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GLP-1 Receptor Agonists

Currently, these agents do not carry an indication for use in PWS

To date, most studies in PWS have involved liraglutide or exenatide

Efficacy of these agents has not yet been proven, results are variable

The gastrointestinal side effects of GLP-1 RAs are a concern for this population

- Diene G, Angulo M, Hale PM, et al. Liraglutide for Weight Management in Children and Adolescents With Prader-Willi Syndrome and Obesity. *J Clin Endocrinol Metab*. 2022;108(1):4-12. doi:10.1210/clinem/dgac549
- Finer N, Strong T, Vrana-Diaz C, Stafford DEJ. Recommendations for real-world evidence of efficacy and safety of GLP-1 agonists in Prader-Willi syndrome: Report of a workshop held by the Foundation for Prader-Willi Research and International Prader Willi Syndrome Organisation. *Diabetes Obes Metab*. Published online November 17, 2025. doi:10.1111/dom.70282
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KNOWLEDGE CHECK 5

Which of the following is a true statement?

A) Liraglutide carries an FDA approved indication for PWS.

B) Results regarding the efficacy of GLP-1 RAs for PWS are variable and their efficacy has yet to be proven.

C) There are no agents in the current pipeline that are exploring an indication for hyperphagia.

D) Pitolisant is primarily being investigated for weight loss in PWS.

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D) Pitolisant is primarily being investigated for weight loss in PWS.

Summary

- PWS is rare a genetic multisystem disorder resulting from certain gene abnormalities in a specific region of chromosome 15
- Given the wide-ranging effects of this condition, individuals with PWS face a multitude of symptoms and comorbidities
- Due to the complexity of this condition, a multidisciplinary team and an array of nutritional, behavioral, and pharmacologic approaches are necessary for management

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Questions?

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