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REVIEW ARTICLE

Prader-Willi Syndrome - Clinical Genetics, Diagnosis and Treatment Approaches: An Update

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Abstract: ***Background*:** Prader-Willi Syndrome (PWS) is a neurodevelopmental genomic imprinting disorder with lack of expression of genes inherited from the paternal chromosome 15q11-q13 region usually from paternal 15q11-q13 deletions (about 60%) or maternal uniparental disomy 15 or both 15s from the mother (about 35%). An imprinting center controls the expression of imprinted genes in the chromosome 15q11-q13 region. Key findings include infantile hypotonia, a poor suck, failure to thrive and hypogonadism/hypogenitalism. Short stature and small hands/feet due to growth and other hormone deficiencies, hyperphagia and marked obesity occur in early childhood, if uncontrolled. Cognitive and behavioral problems (tantrums, compulsions, compulsive skin picking) are common.

***Objective*:** Hyperphagia and obesity with related complications are major causes of morbidity and mortality in PWS. This report will describe an accurate diagnosis with determination of specific genetic subtypes, appropriate medical management and best practice treatment approaches.

***Methods and Results*:** An extensive literature review was undertaken related to genetics, clinical findings and laboratory testing, clinical and behavioral assessments and summary of updated health-related information addressing the importance of early PWS diagnosis and treatment. A searchable, bulleted and formatted list of topics is provided utilizing a Table of Contents approach for the clinical practitioner.

***Conclusion*:** Physicians and other health care providers can use this review with clinical, genetic and treatment summaries divided into sections pertinent in the context of clinical practice. Frequently asked questions by clinicians, families and other interested participants or providers will be addressed.

Keywords: Diagnostic protocols, treatment approaches, genetic testing, genomic imprinting, medication, care management, obesity, caloric intake, Prader-Willi syndrome.

1. INTRODUCTION

Prader-Willi Syndrome (PWS) is a rare complex multisystem genetic disorder recognized as the most commonly known genetic cause of life-threatening obesity in humans [1]. PWS arises from errors of genomic imprinting with lack of expression of paternally inherited imprinted genes in the chromosome 15q11-q13 region generally caused by a paternal deletion or maternal disomy 15 in which both chromosome 15s are inherited from the mother. The cardinal clinical features include severe infantile hypotonia, hyperphagia with the onset of obesity during early childhood if not controlled, developmental delay with learning and behavioral problems, short stature with small hands/feet and hypogonadism/hypogenitalism due to growth hormone and other endocrine deficiencies. Mild craniofacial dysmorphism with enamel hypoplasia and a dry mouth are common. Psychiatric phenotypes, behavioral and autism features correlate with specific PWS genetic subtypes (*e.g.*, autism in those with maternal disomy 15). The collection of findings pose difficult management care issues for families, caregivers and providers. PWS occurs in about 1 in 15,000 individuals *e.g.*, [2-6].

The objective of this review is to provide a searchable bulleted format of terms related to clinical and genetic background information and topics about Prader-Willi syndrome and recommendations for diagnosis and genetic testing, management, treatment and care to guide clinical practice

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throughout the natural history and life span of affected individuals. The shared information is supported by evidence-based medical knowledge obtained from experienced clinicians, cited peer-reviewed published reports and syndrome-specific health care guidelines or best practice recommendations. The importance of early diagnosis and use of a multidisciplinary team will be described and information to be shared will be divided into sections in a bulleted format throughout. Each section represents the clinical presentation and list of features, genetic causation and counseling, diagnostic/genetic testing with therapeutic and management approaches including diet intervention, medication and impact of pharmacogenetics and hormone use with treatment options for behavioral and psychiatric problems most commonly seen in this disorder. These suggested recommendations are intended for health care providers and those assisting in the care and treatment of infants, children and adults with PWS. The clinical and laboratory testing recommendations are based on current medical practice and knowledge, supported by medical evidence reported by clinicians with expertise in PWS along with medical and laboratory geneticists, essential for smooth and effective provisions of care at all ages for those affected with this classic but rare obesity-related genetic disorder. A searchable bulleted format can be accessed by the clinician utilizing the following Table of Contents (Table **1**) to quickly identify pertinent information about clinical presentation, genetics, diagnostic testing and treatment or medical care approaches.

Table 1. Table of contents.

1.1. Key Points

1.1.1. Section Content and Questions to Answer

Bulleted list of clinically important features and genetic aspects of Prader-Willi syndrome are provided based on clinical application, genetic testing options with diagnostic and therapeutic approaches to care.

- Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder characterized by infantile hypotonia, poor suck and feeding difficulty, short stature with small hands and feet, hypogonadism due to growth and other hormone deficiency, mental deficiency, behavioral problems and hyperphagia leading to obesity in early childhood [2-4].

- Individuals with PWS, early in life, display characteristic dysmorphic craniofacial features, including dolichocephaly, a narrow bifrontal diameter, strabismus, a small upturned nose with a thin upper lip and down-turned corners of the mouth, sticky salvia and a dry mouth with enamel hypoplasia.

- Cognitive impairment reduced for family background, behavior problems (temper tantrums, stubbornness, outbursts, self-injury) and psychiatric illness (anxiety and mood disorders, psychosis and autistic spectrum disorder) are observed and correlated with genetic subtypes [2, 3, 7-13].

- Initial clinical consensus diagnostic criteria have been revised and updated; however, confirmation of the diagnosis requires molecular genetic testing for the identification of PWS genetic subtypes [14, 15].

- PWS results from errors in genomic imprinting, most often due to a de novo paternal deletion of the chromosome

15q11-q13 region (about 60% of cases) leading to a lack of expression of paternally derived genes. Maternal disomy 15 or both chromosome 15s inherited from the mother is seen in about 35% of cases. Defects within an imprinting center (micro-deletions, epimutations) in the chromosome 15q11-q13 region or from other chromosome 15q abnormalities account for the disorder in the remaining individuals [3, 5, 16-23].

• Management is most effectively directed by multidisciplinary teams including clinical geneticists, endocrinologists, dietitians, orthopedic specialists, primary care physicians and mental health experts with the goal to control weight gain, monitor and treat associated comorbid conditions, manage behavioral problems and replace growth and other hormone deficiencies [2, 9, 24, 25].

• Rigorous control of the diet and securing the food environment with regular exercise plans are strategies to manage hyperphagia and obesity, complications of which represent the major causes of morbidity and mortality in this disorder [2, 25-27].

1.2. Background

1.2.1. Section Content and Questions to Answer

Case definition with abbreviations, alternative names and references will be provided with cardinal features listed for Prader-Willi syndrome in a bulleted format including distinctive characteristics or a constellation of findings that define this syndrome.

1.3. Description

1.3.1. Genetics and Genetic Subtypes

1.3.1.1 Genetics

• Prader-Willi Syndrome (PWS) is a complex genetic condition that arises due to the lack of expression of genes classified as imprinted on chromosome 15 and are paternally inherited *e.g*., [18].

• In the case of PWS, most of the genes from chromosome 15q11-q13 region are subject to genomic imprinting and only the alleles from the paternally derived chromosome are active. These same alleles from the maternally derived chromosome 15 are silenced by epigenetic factors, primarily through methylation.

• The absence of paternally inherited gene expression from the chromosome 15q11-q13 region gives rise to the PWS phenotype and syndrome.

• Most PWS cases are sporadic, generally from a paternal 15q11-q13 deletion, but familial cases can occur in situations where the father contributes a microdeletion of the imprinting center received from his mother, but this is uncommon. Imprinting center defects (microdeletion or epimutation) occur in less than 3% of PWS families. Under these circumstances, additional children with PWS may result with the risk of recurrence at 50% [3, 21, 28].

1.3.1.2. Genetic Subtypes

Chromosome 15q11-q13 Deletions in Prader-Willi Syndrome.

• About 60% of PWS individuals will show a de novo typical paternal deletion of the 15q11-q13 region consisting of two types, type I and type II [1, 11].

• The type I deletion is larger and involves chromosome 15q proximal breakpoint, BP1 and distal breakpoint, BP3 [21].

• The type II deletion is smaller and involves chromosome 15q proximal breakpoint, BP2 and distal breakpoint BP3.

• In about 5% of PWS individuals, an unusual or atypical deletion is seen which is greater or smaller in size than the typical type I or type II deletion [3, 5, 23, 29-31].

Maternal Disomy 15 in Prader-Willi Syndrome

• The second most common genetic cause of PWS is found in about 35% of individuals and referred to as maternal disomy 15 where both chromosome15s come from the mother. Genes on chromosome 15 inherited from the mother are normally silenced by epigenetic factors, primarily through methylation and consists of three recognized disomic types:

• Maternal heterodisomy 15 with two different chromosome 15s from the mother due to errors in meiosis I from homologous chromosome nondisjunction and no crossover events.

• Maternal isodisomy 15 with two identical chromosome 15s from the mother due to errors in meiosis II from nondisjunction.

• Maternal segmental isodisomy 15 with two partially different chromosome 15s from the mother due to errors in meiosis I from nondisjunction and crossover events leading to segments of isodisomy or loss of heterozygosity [3-5, 23].

• Older mothers have a greater chance of having a child with PWS and maternal disomy 15 compared with those having the typical 15q11-q13 deletion [23].

1.3.2. Cardinal Clinical Features and Presentation

Cardinal clinical features.

• Craniofacial anomalies.

• Intellectual disability.

• Infantile hypotonia.

• Growth hormone deficiency.

• Hypogonadism/Hypogenitalism.

• Behavioral problems.

• Hyperphagia leading to obesity in early childhood.

1.3.3. Clinical Course Development and Presentation

The course of PWS is historically divided into two clinical stages with failure to thrive representing the first stage and hyperphagia with the onset of obesity representing the second stage. Recent studies have shown more gradual and complex progression with the development of nutritional phases, as outlined below.

• Prenatal features include reduced fetal activity (88%), breech presentation and non-term delivery. Other characteristics of the fetal phenotype include small for gestational age

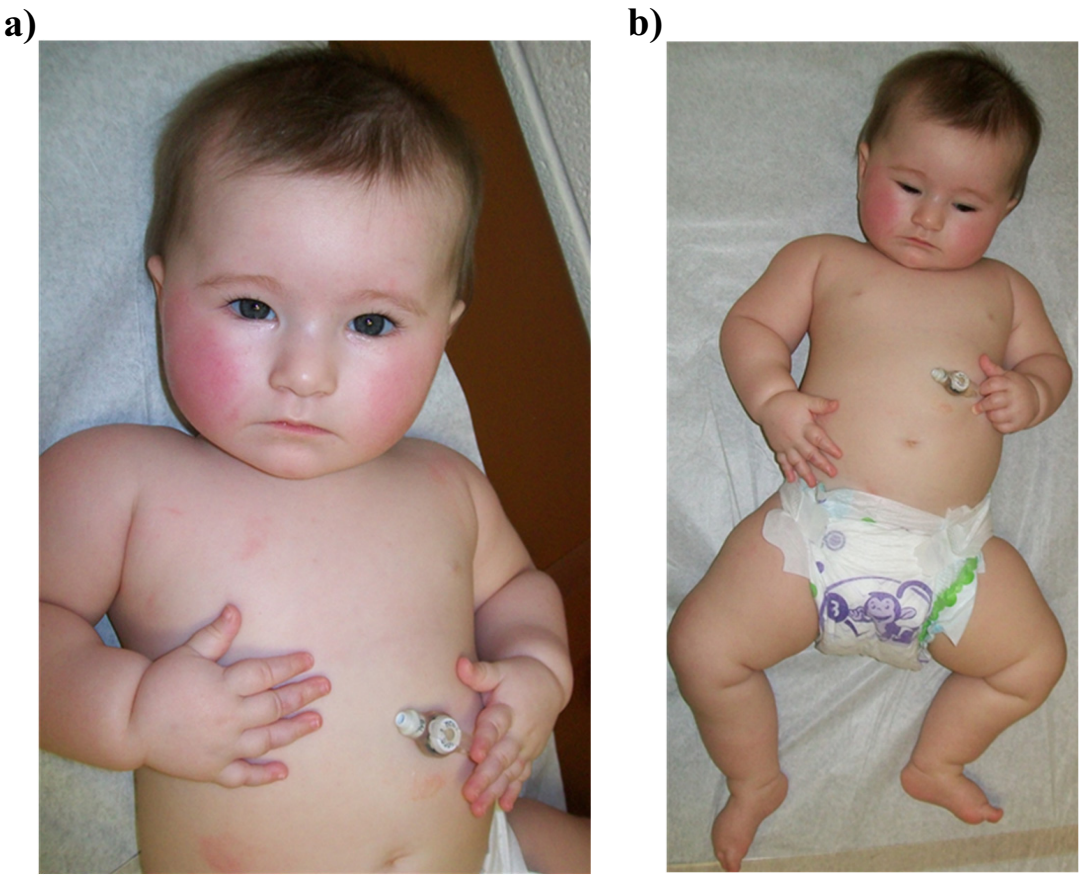

Fig. (1). (**a**). Facial and torso view of a 9 month-old female with Prader-Willi syndrome due to a 15q11-q13 deletion. Note the narrow bifrontal diameter, almond-shaped eyes, a flaccid appearing face, down-turned corners of the mouth, a small chin and short neck frequently seen in PWS infants. A gastrostomy feeding site is observed in the upper abdomen. (**b**). Frontal body view of the infant female with Prader-Willi syndrome. Note generalized hypotonia and gastrostomy site related to a poor suck, hypotonia and feeding difficulties.

(65%) and increased head/abdomen circumference ratio (43%). Polyhydramnios is also noted (34%) and probably reflects inability to coordinate suck and swallow which appears after 36 weeks in typical fetuses. Pre- and post-term delivery is also noted in PWS pregnancies particularly in those with babies that have maternal disomy 15 [32-34].

• Features of PWS are evident at birth including infantile hypotonia, feeding problems with a poor suck, hypopigmentation, hypogonadism/hypogenitalism with hypoplastic clitoris and labia in females and a small penis with cryptorchidism in males [1, 35-37]. During infancy feeding problems and hypotonia persist with decreased muscle mass and strength, developmental delay, temperature instability and growth hormone deficiency resulting in short stature with small hands and feet [5].

• Craniofacial findings seen in PWS include dolichocephaly, a narrow minimal frontal diameter, strabismus, almond-shaped eyes, short upturned nose with thin upper lip and downturned corners of the mouth with sticky salvia and enamel hypoplasia [1, 2, 35-37].

• As the patient enters the preschool years, additional behavioral characteristics emerge including temper tantrums, increased interest in food and eventually increased food seeking with weight gain if food access is not controlled. Developmental delays are common and may require specialized services. Intellectual delay and learning problems are apparent by school age. Repetitive asking, cognitive rigidity, compulsive and disruptive behavior are common. Episodic skin excoriation occurs in about 60%; perpetuating factors including poor self-awareness with decreased pain sensitivity (Fig. **1** of an infant with PWS).

1.3.4. Nutritional Phases in PWS

Historically, PWS is described as having two clinical stages (*i.e.* failure to thrive then followed by hyperphagia leading to obesity) but recent classification schemes based on natural history studies, have proposed five main nutritional phases highlighted by the gradual and complex progression of this disorder. Progression through the nutritional phases may be altered by the use of growth hormone treatment beginning at a young age.

• Phase 0: Occurs in utero with decreased fetal movement and growth restriction.

• Phase 1: Hypotonic, non-obese infant (birth to 15 months of age).

- Subphase 1a: Difficulty feeding with or without failure to thrive.
- Subphase 1b: Steady infant growth and weight gain along a representative growth curve.

- Phase 2: Weight gain begins (~2 years of age).
  - Subphase 2a: Weight increases without change in appetite or caloric intake.
  - Subphase 2b: Weight gain occurs with increased interest in food.

- Phase 3: Hyperphagia and lack of satiety accompanied by food seeking (~8 years of age).
- Phase 4: Appetite is no longer insatiable [26].

2. MATERIALS AND METHOD

A searchable bulleted formatted list of clinically important features and genetic aspects of Prader-Willi syndrome is provided along with diagnostic approaches and treatment/medical care plans for the practicing physician or health care provider using a Table of Contents approach to find information needed for the care and treatment of a patient with Prader-Willi syndrome. An extensive review was undertaken searching published reports from the literature, textbooks and medical practice guidelines with recommendations generated by clinicians and established organizations/groups experienced with screening prevention, diagnosis and treatment options for patients with this rare obesity-related genetic disorder. This pertinent information was collated and arranged in sections that can be searchable as needed at the time of patient care in the clinical setting to address specific questions/issues such as key points, causes and risk factors, clinical presentation, diagnosis/laboratory evaluation, specific tests, consultation, treatment and medications, patient satisfaction/lifestyle priorities, prognosis, complications and guidelines.

3. RESULTS AND DISCUSSION

3.1. Epidemiology

3.1.1. Section Content and Questions to Answer

Gender, age group and ethnicity will be identified with quantitative data on incidence/ prevalence in a bulleted format.

3.1.1.1. Introduction and Background

- The estimated prevalence of PWS is 1 in 10,000 to 20,000 individuals with a reported range of 1 in 8,000 to 1 in 30,000. The number of individuals worldwide with PWS is estimated at 400,000 and about 20,000 individuals in the USA [1, 37].

- Most cases of PWS are sporadic with an approximate 1:1 gender ratio. All ethnic groups are represented, but PWS is reported disproportionately more in Caucasians [38]. Based on population studies, the death rate in PWS is estimated at 3% per year [39].

- Prader-Willi syndrome is the most common known genetic cause of life-threatening obesity in humans [1, 2].

- In a large survey of causes of death in PWS, the top causes were respiratory failure (31%), cardiac (16%), gastrointestinal (10%), infection (9%), obesity (7%), pulmonary embolism (7%), choking (6%) and accidents (6%) [40]. The average age of death in the 486 individuals with PWS reported in 2017 was 29.5 years; 80% of those who died were older than 18 years of age.

3.2. Causes and Risk Factors

3.2.1. Section Content and Questions to Answer

Specific causes and comorbidities of PWS will be listed in order of importance and specific risk factors or predisposing circumstances discussed. Causes will be considered when a direct etiologic role and risk or predisposing factors are known and described using a bulleted format.

3.2.1.1. Causes

- Prader-Willi syndrome is due to errors in genomic imprinting involving the long arm of chromosome 15 leading to the loss of expression of paternally derived genes. These imprinted genes are present on the maternal chromosome 15 but are normally inactivated [21].

- The most common event is a due to de novo paternal deletions of 5-6 Mb in size from the chromosome 15q11-q13 region and occurs in 60% of PWS cases [41].

- Maternal disomy 15 (both chromosome 15s are contributed by the mother) occurs in about 35% of the cases [5, 21].

- An imprinting center defect (microdeletion or epimutation) or other chromosome 15q abnormality (*e.g.*, translocation or inversion) accounts for the minority of cases (5% or fewer) [21].

- PWS individuals with maternal disomy 15 having the isodisomy or segmental isodisomy forms are at risk for secondary genetic conditions involving recessive genes on chromosome 15 if the mother is a recessive gene carrier. Several hundred recessive genes are known to be present on chromosome 15 causing different types of health problems such as hearing loss, cardiac abnormalities, seizures or metabolic defects. In addition, PWS females with maternal disomy 15, due to trisomy 15 rescue in early pregnancy may develop X-linked genetic conditions. This results from non-random X chromosome inactivation skewness in which the X chromosome carrying the abnormal X- linked gene is active in the majority of cells (*e.g.*, >80%) [3, 32, 35, 42].

- Studies are underway using animal models [43], measures of neuropeptides (*e.g.* oxytocin, substance P, neurotensin) [44-47], development of pluripotent stem cells [48], functional MRI scans to examine eating and aberrant behavior in PWS [49] and clinical trials targeting hyperphagia.

3.2.1.2. Risk Factors

- As with other numerical chromosome syndromes (*e.g.*, Down syndrome due to trisomy 21), there is a correlation with advanced maternal age and trisomic 15 fertilized eggs (zygotes) due to maternal meiosis errors (nondisjunction) and trisomy rescue in early pregnancy. Trisomy 15 rescue event leads to maternal disomy 15 and PWS by reducing the chromosome count of 47 to a normal 46 but with two chro-

mosome 15s from the mother with loss of the chromosome 15 from the father in subsequent cells in the developing fetus [34, 50].

• Hydrocarbons are known to cause chromosomal damage in human cell cultures. Early reports of over-representation of fathers with occupations associated with exposure to hydrocarbons were noted among children who develop PWS and concerns raised about possible increased incidence in highly industrialized and environmentally unregulated regions of the world.

• Research has shown a correlation with Assisted Reproductive Technology (ART) and imprinting disorders such as Beckwith-Weidemann syndrome due to interference with the methylation DNA pattern required to control normal gene activity and may impact the occurrence of PWS, as well [51, 52].

3.3. Associated Disorders Ordered by Importance

3.3.1. Section Content and Questions to Answer

Comorbid conditions are included that tend to occur in the same patient as the index disease such as PWS and may be linked to the index disease by etiology or by common risk factors but not linked in a cause/effect relationship. Conditions that predispose to Prader-Willi syndrome or develop from it or other conditions that frequently accompany PWS will be addressed.

3.3.1.1. Introduction and Background

• Orthopedic problems include hip dysplasia or subluxation (in 10% or higher) noted at birth or later in infancy and scoliosis which appears to be bimodal with development prior to 4 years of age with infantile spinal curvature and later in childhood or early adolescence (in 40% or higher). About two-thirds of patients with PWS will be affected by the time of skeletal maturation. Most individuals with PWS present with lumbar or thoracolumbar curves in comparison with those having idiopathic scoliosis without PWS where the typical location is thoracic. Most patients with PWS have Growth Hormone (GH) deficiency and require GH therapy offered at the time of diagnosis by genetic testing. Bracing or surgical intervention may also be needed. Osteoporosis and osteopenia are common and can lead to stress fractures but may be prevented with adequate nutritional intake of calcium/vitamin D and physical activity to stimulate bone health with endocrine therapy. Growth hormone and sex steroid hormone deficiencies, commonly seen in this disorder, are contributing factors. Orthopedic complications should be monitored closely particularly during growth hormone (GH) treatment commonly in use in PWS infants, children and adolescents to treat short stature, impact positively on lean body mass, decrease fat and improve physical activity. As these children may develop scoliosis as a component of this syndrome, radiological skeletal surveys for scoliosis should begin at about 18 months of age and monitored consistently [2].

• Other endocrine disturbances, besides growth hormone deficiency, include hypothyroidism and central adrenal insufficiency seen in about 10% of individuals with PWS [2, 53, 54]. Insulin resistance and type 2 diabetes can be seen with overweight/obesity status.

• An increased risk of seizures is noted.

• Temperature instability is common during infancy and childhood with a possible lack of febrile response even with severe infections [2]. Adolescents and adults with PWS have been reported to have body temperatures below 90º F. Hypothermia is related to decreased peripheral perception of pain and cold temperature in PWS [55]. Infection or hypothyroidism should be ruled out, but the most common cause is iatrogenic due to medications (atypical antipsychotics or beta blockers). Serious medical sequelae include prolonged bleeding time, myocardial abnormalities (bradycardia, dysrhythmia, conduction defects), decreased metabolism of medications, decreased kidney function with disturbed acid/ base balance and altered mental status. Idiopathic hyper or hypothermia may occur during minor illnesses and during anesthesia [56]. PWS individuals may not respond normally to infection regarding bodily temperatures [2].

• Autonomic nervous system dysfunction contributes to dry mucosal membranes and decreased salivary flow common in individuals with PWS at all ages. It predisposes to baroreflex abnormalities and decreased heart rate variability seen in PWS [2].

• Periodic breathing with central apneas is increased in frequency in infants with PWS with desaturations worse in rapid eye movement (REM) sleep along with narcolepsy-like symptoms [2].

• Adenotonsillar hypertrophy, obesity, craniofacial abnormalities and neuromuscular weakness are risk factors for obstructive sleep apnea (OSA). Sleep studies are indicated to determine the presence and severity of OSA, prior to and up to 3 months after initiating GH treatment, prior to spinal fusion/instrumentation for scoliosis, or as part of an evaluation to identify the cause of excessive daytime sleepiness [2].

• GABA receptor gene subunits which are not imprinted but located in the chromosome 15q11-q13 region are commonly deleted in PWS; therefore, neurotransmitter disturbances may be present. In addition, reduced expression of GABA receptor subunits could alter the response to anesthesia or sedative agents such as propofol. PWS patients should be monitored closely before, during and after surgery to avoid complications from anesthesia [21, 56].

• PWS individuals with maternal disomy 15 are at risk for secondary genetic conditions involving recessive genes on chromosome 15 if the mother is a carrier. In addition, PWS females with maternal disomy 15 due to trisomy 15 rescue in early pregnancy may develop X-linked genetic conditions due to non-random X chromosome inactivation skewness. If the father is a carrier of an imprinting defect such as a microdeletion then genetic testing and counseling can be offered to rule out the presence of the defect in a newborn sibling or for prenatal diagnosis. Fathers carrying the genetic imprinting defect due to a microdeletion would be at a 50% risk of passing on the defect to his offspring leading to PWS [3-5].

3.4. Complications Related to Prader-Willi Syndrome

PWS is associated with findings related to hyperphagia and obesity if access to food and weight is not adequately controlled. These include:

3.4.1. Prader-Willi Syndrome

- Diabetes mellitus.
- Osteoporosis.
- Right-sided heart failure.
- Fatty liver.
- Hypoventilation.
- Obstructive sleep apnea and narrow airway.
- Stasis ulcers and cellulitis.
- GI dysmotility involves abnormalities of chewing and swallowing that predispose to risk of choking; esophageal dysmotility that predisposes to rumination, GERD and silent aspiration; delayed gastric emptying that predisposes to gastroparesis; and constipation. Antecedents to gastroparesis include excessive food intake, gastroenteritis, constipation, or a change of diet in persons of any age. Individuals with PWS have a high pain threshold and lack of vomiting, therefore they may not respond normally to abdominal distention or pain from life-threatening gastric inflammation or necrosis [2, 57]. A refusal to eat or foul smelling eructation may be the only sign.
- Water intoxication and electrolyte imbalances (*e.g*., dilutional hyponatremia) can occur due to excessive fluid intake or low vasopressin levels with fluid retention, or medications such as diuretics and antidepressants, interfering with electrolyte levels [2].

3.5. Population at Risk or Screening Modalities

3.5.1. Section Content and Questions to Answer

Briefly, an outline is given for whom and how to screen and guideline-based recommendations cited for screening when appropriate using a bulleted format. Specific group(s) are identified for screening and why to screen including a list of screening measures and their description.

3.5.1.1. Introduction and Background

- No specific groups are at risk or should be screened but an over-representation of Caucasian patients with PWS has been reported.
- No screening for PWS among the general population is currently available but newborn screening approaches have been raised and maybe feasible using both methylation testing and chromosome deletion assays [58].

3.6. Preventive Measures

3.6.1. Section Content and Questions to Answer

Briefly, an outline with measures for prevention and to whom they apply will be cited in bulleted format.

There is no recognized approach to prevent the risk of lowering the chance of having a child with Prader-Willi syndrome. PWS occurs at random but an association is found with advanced maternal age in those PWS children with maternal disomy 15.

3.7. Clinical Presentation and Testing

3.7.1. Section Content and Questions to Answer

Short and succinct summary of entire diagnostic approach mentioning clinical presentation (symptoms and signs) and testing strategy will be produced and discussion of test results impacting on disease management in bulleted format. Standard criteria for diagnosis, diagnostic guidelines and severity classifications will be provided including an approach for diagnostic evaluation and syndromic features with specialized tests and their descriptions.

3.7.1.1. Introduction and Background

- The clinical presentation of PWS has historically been divided into two distinct clinical stages with failure-to-thrive and feeding problems representing the first stage and onset of obesity representing the second stage [1].
- During the perinatal period, reduced fetal activity, polyhydramnios, breech presentation and non-term delivery are often observed.
- During infancy, PWS is characterized by hypotonia, feeding problems with a poor suck reflex, temperature instability, central sleep apnea, decreased muscle mass and strength and developmental delay.
- PWS craniofacial findings include dolichocephaly or a narrow head shape, a narrow minimal diameter, strabismus, almond-shaped eyes, short upturned nose with thin upper lip and downturned corners of the mouth with sticky salvia and enamel hypoplasia. Physical findings include hypopigmentation, hypogonadism/hypogenitalism (with hypoplastic clitoris and labia in females and a small penis and cryptorchidism in males) and growth hormone deficiency with short stature and small hands and feet and developmental delay.
- During early childhood (about 2 to 6 years of age), additional features appear including temper tantrums, food seeking behavior and hyperphagia leading to obesity, if not controlled by calorie management and restricting food access.
- Mental deficiency, learning problems, behavioral problems including repetitions, compulsions, emotional outbursts and skin picking complicated by a high pain threshold, also develop during childhood [2-4, 9, 10, 59].

3.7.1.2. Testing Strategy

- Consensus diagnostic criteria have been established for PWS based on clinical presentation and should be fulfilled to support a diagnosis of PWS [14].
- Genetic testing by an appropriately licensed laboratory is mandatory to confirm the diagnosis of PWS when suspected on clinical grounds. Early diagnosis in infancy using accredited genetic testing should be sought and allows early intervention.

• Molecular testing should include DNA methylation analysis and detection of the chromosome 15 deletion (or other chromosome 15 anomalies).

• Findings that should prompt genetic testing for PWS, classified by age, include:

o Birth to age 2: Hypotonia with a poor suck and feeding problems with inadequate weight gain should trigger testing for PWS using current molecular genetic testing assays for PWS.

o Ages 2-6: History of congenital central hypotonia, a poor suck and global developmental delay.

o Ages 6-12: History of hypotonia with a poor suck, global developmental delay, food foraging with hyperphagia and central obesity. Premature adrenarche is common but premature puberty is not.

o Ages 13 years through adulthood: Cognitive impairment, preoccupation with food, hyperphagia with central obesity, behavioral problems (*e.g.*, temper tantrums, self-injury) and hypogonadotropic hypogonadism.

3.7.1.3. Pharmacogenetics Testing

• Genetic testing for pharmacogenetics and its role in medication selection and management is now used as a personalized medicine approach in the clinical setting. Pharmacogenetics is the study of inherited genetic differences in drug metabolic pathways in terms of therapeutic effect as well as adverse outcomes. The roles of specific genes encoding proteins impacting drugs/medications along with their inhibitors and inducers relate to the field of pharmacogenetics and function of the Cytochrome (CYP) p450 hepatic enzymes to breakdown drugs. Pharmacodynamic factors such as neurotransmitter and transporter polymorphisms can also inform psychotropic medication response.

3.7.1.4. Molecular Analysis

• Molecular testing for PWS should begin with DNA methylation analysis of a blood specimen, but will not identify the specific genetic subtype. If the DNA methylation test is normal, then other clinical disorders should be considered.

• A chromosome analysis with fluorescence in situ hybridization (FISH) will identify the typical 15q11-q13 deletion but preferably a DNA chromosomal microarray analysis should be performed using both Copy Number Variant (CNV) and single nucleotide poly- morphism (SNP) probes to identify not only the size of the 15q11-q13 deletion (typical and atypical) but helpful for determining the maternal disomy 15 subtype status by identification of Loss of Heterozygosity (LOH) of chromosome 15 gene alleles [23, 41, 60].

• If methylation testing shows a PWS methylation pattern and no recognizable 15q11-q13 deletion, then genotyping with polymorphic chromosome 15 DNA markers may be needed to identify biparental (normal) inheritance of chromosome 15 indicating an imprinting defect, if DNA chromosomal microarray analysis with CNV and SNP probes did not identify a deletion or extensive LOH (*e.g.*, >8Mb in size) on chromosome 15 indicating maternal disomy 15 status [23, 60].

• Droplet Digital PCR is a new genetic technology that can be applied to PWS by identifying small deletions as well as for gene expression studies. It has the potential to identify whether mosaicism exists in an individual with PWS by examining the methylation status or gene expression patterns. There is evidence that some individuals that some individuals with PWS may have a mixture of normal and abnormal PWS methylation or gene expression patterns which may be helpful for medical care and diagnosis, specifically in those with PWS and maternal disomy 15 [23, 60].

3.7.1.4.1. Clinical Symptoms

• Hyperphagia - Begins in early childhood or later.

• Lack of satiety.

3.7.1.4.2. Clinical Signs

• Mild prenatal growth retardation - Birth weight, length and body mass index (BMI) are reduced by 15% compared to unaffected siblings.

• Hypotonia- Prenatal hypotonia is evident by reduced fetal movement. Infantile hypotonia (central origin) is evident by reduced movement, hypoarousal and a weak cry with poor suck and feeding problems.

• Poor suck and lethargy result in failure to thrive.

• Global developmental delay and mental deficiency (average IQ=65) occur in nearly all children with PWS in relationship to family background. Studies have shown that verbal comprehension is higher in maternal disomy 15 compared to the 15q11-q13 deletion subtypes, but adaptive function rarely reaches the level predicted by verbal IQ.

• Dysmorphic craniofacial findings - dolichocephaly, a narrow minimum frontal diameter, strabismus, almond-shaped eyes, short upturned nose with thin upper lip and downturned corners of the mouth.

• Hip dysplasia and subluxation in infants.

• Thick viscous saliva.

• Food foraging, hoarding and stealing.

• Excessive and rapid weight gain leading to obesity.

• Short stature.

• Small hands and feet.

• Narrow hands with straight ulnar border.

• Kyphosis, lordosis and anterior head tilt (adolescence and adulthood).

• Hypopigmentation.

• Genital hypoplasia.

• Myopia.

• Enamel hypoplasia, dental caries and dry mucosal membranes; dental erosion due to bruxism.

• Skin picking can be problematic particularly at a surgical site or in a covered area (*e.g.*, perianal abscess).

3.7.1.4.3. Clinical Findings

• Behavioral and psychiatric disturbances.

- Impulsivity, aggression, food theft, property destruction and self-injury.
- Cognitive rigidity leading to emotional outbursts, tantrums and oppositional behavior.
- Repetitive and compulsive behaviors, such as collecting and hoarding, together with cognitive rigidity become more problematic in adolescence and young adulthood along with depression, anxiety and in some cases bipolar disorder or psychosis.
- Food-related activities such as food seeking, stealing and hoarding, eating non-food items (*e.g*., dog food), searching in garbage cans, stealing money to buy food and running away from home to access food.
- Scoliosis.
- Speech articulation defects with hypernasal tone.
- Dysphagia, choking and silent aspiration.
- Sleep disturbances, including central and obstructive sleep apnea.
- Osteoporosis.
- Decreased vomiting.
- High pain threshold.
- Temperature instability.
- Growth hormone deficiency.
- Hypothyroidism in about 10% of individuals with PWS and similarly for central adrenal insufficiency.
- Early adrenarche, but rarely premature puberty.
- Hypogonadism - Mixed primary and central (hypothalamic) components, but the latter predominate.
- Incomplete and/or delayed pubertal development.
- Infertility - Pregnancies and livebirths have been reported rarely in females with PWS; gonadotropin and inhibin B levels are the best predictors for fertility in females. Males are presumed to be infertile because inhibin levels decline with age, but examination of ejaculate for spermatozoa is the best determinant.
- Academic difficulties beyond that expected for level of ability, often reflecting additional learning disabilities in focused areas.

Fig. (**2**) illustrates the classical features seen in a 16 year -old female with PWS not treated with growth hormone.

3.8. Clinical Consensus Diagnostic Criteria

Consensus diagnostic criteria for PWS have been reported and revised with updates based on clinical findings and presentation [14, 15].

For children under 3 years of age, five of the clinical diagnostic criteria points are required, three of which must come from the major criteria category. For those older than 3 years of age, eight of the clinical diagnostic criteria points are required, four of which must come from the major criteria category. Supportive criteria do not contribute to the point total will require 8 points (with 4 from the major criteria category).

3.8.1. The Major Criteria Include

- Neonatal and infantile hypotonia.
- Feeding problems and failure to thrive in infancy.
- Excessive or rapid weight gain with onset between 12 months and 6 years of age.
- Characteristic facial features.
- Hypogonadism.
- Global development delay and mild to moderate mental retardation.
- Hyperphagia.

3.8.2. The Minor Criteria Include

- Decreased fetal movement.
- Characteristic behavior problems.
- Sleep disturbances/ sleep apnea.
- Short stature.
- Hypopigmentation.
- Small hands and feet.
- Narrow hands with straight ulnar border.
- Eye abnormalities.
- Thick viscous saliva.
- Speech articulation defects and skin picking.

3.8.3. Supportive Findings Include

- High pain threshold.
- Decreased vomiting.
- Temperature instability.
- Scoliosis and/or kyphosis.
- Early adrenarche.
- Osteoporosis.
- Unusual skill with jigsaw puzzles.
- Normal neuromuscular studies.

Formal genetic testing for confirmation of the clinical diagnosis of PWS is still required and this should include (1) DNA methylation analysis; and (2) detection of the chromosome 15 deletion or other chromosome 15 anomaly.

3.9. Laboratory Evaluation

3.9.1. Section Content and Questions to Answer

A summary approach is provided for diagnostic evaluation, outlining of tests and imaging. Specific tests are followed by subsections on each test to include: Description, normal results and comments with evidence-based medicine (EBM) entries at the end of each test subsection, if indicated. EBM entries are summarized with relevant results and most important statistical values. The sensitivity and specificity for the most important tests are given along with supportive

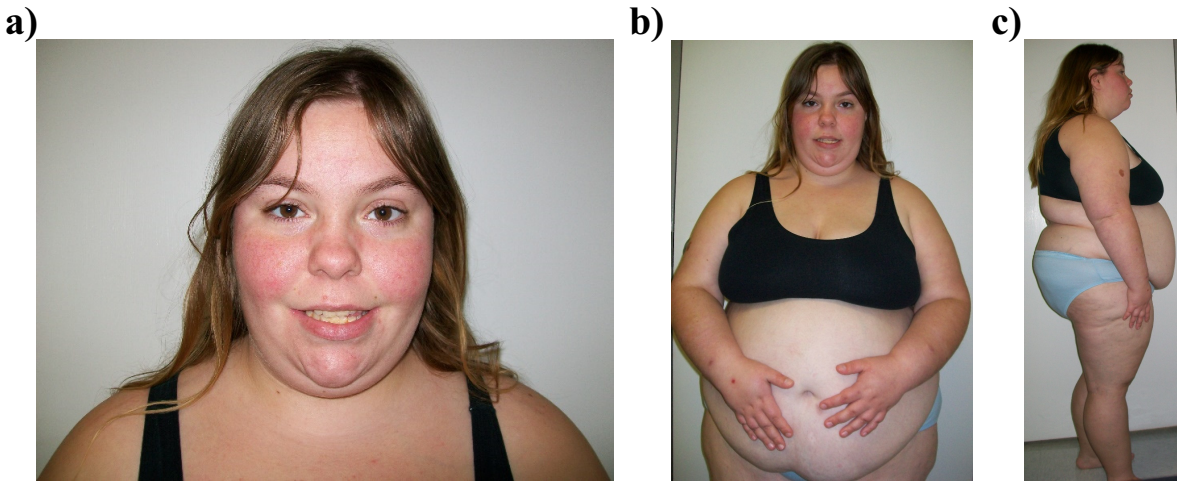

Fig. (2). (**A**). Facial view of a 16 year-old female with Prader-Willi syndrome due to maternal disomy 15 without growth hormone treatment. Note slightly upward slant of almond-shaped eyes, a short nose and short neck with obesity. (**B**). Frontal view of face and torso of the 16 year-old female with Prader-Willi syndrome showing characteristic facial findings, central obesity and self-injury sites on right hand and wrist. (**C**). Full body profile of the 16 year-old female with Prader-Willi syndrome showing obesity and small hands commonly seen in this obesity-related genetic disorder.

evidence. Other tests that might important for designing a management strategy are discussed.

3.9.2. Summary of Test

• Several laboratory tests are necessary for the molecular diagnosis and subtyping of PWS. A stepwise approach to utilizing these tests is recommended with the first step to confirm the clinical suspicion for PWS using DNA methylation analysis. The second step is to determine the cytogenetic or molecular class (*i.e.*, the specific genetic lesion involving chromosome 15).

• Options for DNA methylation analysis now include polymerase chain reaction (PCR) along with Southern blotting of the SNRPN probe for the chromosome 15q11-q13 region or Methylation-Specific Multiplex Ligation-Dependent Probe Amplification (MS-MLPA) approaches utilizing several imprinted probes from this chromosome region. If the methylation result is abnormal (as found in 99% of PWS individuals), then historically FISH (fluorescence in situ hybridization) analysis would be ordered to identify the deletion status and to rule out a translocation or other chromosome 15 anomaly. Currently, DNA microarrays with SNP and CNV probes or MS-MLPA kits and in addition newly described Droplet Digital PCR technology can be used to determine the deletion status [presence (and size) or absence] performed at any age for the patient [3-5, 61-64].

• Molecular analysis for maternal disomy 15 (the second most common genetic cause of PWS) should be undertaken if the deletion status is normal and methylation is abnormal (PWS pattern). Chromosomal microarrays with SNP and CNV probes can assist in determining the maternal disomy 15 subclass status (heterodisomy, isodisomy or segmental isodisomy) in a significant number of those with maternal disomy 15. Genotyping DNA markers located throughout the long arm of chromosome 15 will allow for determination of the parental source of the chromosome 15s (normal biparental inheritance or maternal disomy 15) if chromosomal microarrays are not informative by not showing isodisomy 15 or segmental isodisomy 15 and paternity status is established [23]. In a study of 510 individuals with PWS, 303 (60%) had 15q11-q13 deletion, 185 (36%) had maternal disomy 15 and 22 (4%) had imprinting center defects [23].

• If necessary, additional testing may be required to identify the type of imprinting defects (microdeletion or epimutation), which represents the third genetic subtype seen in PWS (~3% of patients). This type of testing is typically conducted in research settings.

• DNA methylation analysis is the initial molecular test to confirm the diagnosis of PWS.

• Methylation-Specific Multiplex-Ligation Probe Analysis (MS-MLPA) is performed to determine the molecular class and DNA methylation status (*i.e.*, the specific genetic lesion involving chromosome 15) [63, 64].

• Fluorescence *In-situ* Hybridization (FISH) with high resolution karyotype may be ordered to identify the deletion status and to rule out a translocation or other chromosome 15 anomaly but used less often with advances in genetic testing such as chromosomal microarrays or Droplet Digital PCR, a new genetic method used to identify small deletions or changes in gene expression in PWS. This method can also be used to identify low grade mosaicism in those individuals with PWS and maternal disomy 15 [61].

• Chromosomal microarray (CMA) in high resolution uses hundreds of thousands of single nucleotide polymorphism (SNP) and Copy Number Variant (CNV) probes to determine the presence and size of a chromosome deletion as well as to determine the presence of maternal disomy 15 subclass status (heterodisomy, isodisomy or segmental isodisomy) depending on level or size (>8mb) of loss of heterozygosity or regions having lack of polymorphic DNA marker signals due to crossover events in meiosis I in female gametogenesis in the mothers of these children with PWS and maternal disomy 15. If the mother is a carrier of a mutation of a recessive gene on chromosome 15 in the isodisomic region, then the PWS child could also have a recessive genetic condition

in addition to PWS such as Bloom syndrome or Tay-Sachs disease [23, 35].

• DNA polymorphism or genotype analysis using chromosome 15 DNA markers can be performed to determine whether the inheritance pattern is biparental (normal) or maternal-only (maternal disomy).

• DNA sequence analysis is reserved for rare situations after DNA methylation analysis (maternally methylated allele only), FISH (no deletion), quantitative microsphere hybridization [22] and DNA polymorphism analysis (biparental inheritance) have been performed [62].

• Adrenal reserve assessment is performed to assess for central adrenal insufficiency in PWS prior to growth hormone therapy.

• Complete thyroid function tests are performed to assess for hypothyroidism, particularly prior to initiating GH therapy even in the presence of normal thyroid screening at birth.

• Liver function testing and serum Insulin-like Growth Factor-1 (IGF-1) levels are used to assess for growth hormone deficiency and to monitor GH replacement therapy on a regular basis (*e.g*., every 3 months with IGF-1 levels) [65].

• Fasting blood glucose and oral glucose tolerance tests are used to assess for diabetes.

• Dual X-ray absorptiometry (DXA) scan is used to evaluate bone mineral density and body composition [66].

• Polysomnography is performed to assess for sleep apnea prior to growth hormone treatment and after 3 months treatment in infancy [2]. MSLT (multiple sleep latency test) is required to diagnose narcolepsy.

• Baseline spine radiographs are obtained to assess for scoliosis beginning at about 18 months of age and for periodic evaluation subsequently depending on the onset of GH treatment. Ultrasound or radiographs of the hips can be obtained as soon as the child can sit. Skeletal findings and growth rate may depend on family history and Growth Hormone Receptor (GHR) gene polymorphism status which has been shown to impact growth rate on PWS and control individuals while treated with GH [2, 67].

• PWS specific growth charts for growth hormone treated and non-treated patients with PWS are available from 0 to 18 years of age to be used in the clinical setting to monitor growth patterns and response to growth hormone therapy in those affected with this syndrome [68-70] and available at:

http://www.pwsausa.org/wp-content/uploads/2017/01/Ht-wt-GH-treated-girls-3-18y-2016.pdf

http://www.pwsausa.org/wp-content/uploads/2017/01/HC-GH-treated-boys-2016.pdf

http://www.pwsausa.org/wp-content/uploads/2017/01/HC-GH-treated-girls-2016.pdf

3.10. Specific Genetic Laboratory Tests

3.10.1. Single Probe DNA Methylation Analysis

DNA methylation for PWS can be done utilizing three methods historically. Southern blotting with chromosome15 methylated DNA probes; methylation specific PCR (mPCR) using single chromosome 15 methylated DNA probes (*i.e*., SNRPN) and MS-MLPA kits provided with multiple methylation sensitive DNA probes from the 15q11-q13 region.

3.10.1.1. Description

• A venous blood sample from the proband must be collected for DNA extraction and isolation.

• Genetic testing technique that uses the principle of epigenetics or the differential DNA methylation of imprinted loci to assess for paternal-only, maternal-only and biparental (normal) inheritance.

• Southern blot or methylation-specific Polymerase Chain Reaction (mPCR) utilizing single methylation-related probes [62].

• The most robust, latest generation assays available target the carboxy-terminal CpG island of the SNRPN locus.

3.10.1.2. Normal Results

• DNA from normal individuals will have both a methylated (maternally inherited) and an unmethylated (paternally inherited) allele.

3.10.1.3. Comments

• Most efficient test to start the genetic work up if PWS is suspected as it will identify PWS in > 99% of cases [3].

• Test cannot distinguish the molecular class (*i.e*., deletion, uniparental disomy or imprinting defect); therefore, additional tests are needed if the methylation pattern is maternal-only inherited (a result that is indicative of PWS) [2].

3.10.2. Methylation-specific Multiplex-ligation Probe Analysis (MS-MLPA)

3.10.2.1. Description

• A venous blood sample from the proband must be collected for DNA extraction and isolation.

• Utilizes commercially available MS-MLPA kits which include multiple probes to detect DNA methylation differences in the 15q11-q13 region for diagnosis of Prader-Willi syndrome [61, 63, 64].

3.10.2.2. Normal Results

• DNA from normal individuals will have both a methylated (maternally inherited) and an unmethylated (paternally inherited) allele.

3.10.2.3. Comments

• MS-MLPA is a genetic test technique that is used to determine methylation status of the PWS region and can also detect genomic deletions or duplications. It combines the technique of DNA methylation analysis and gene dosage analysis using multiple specific probes across the PWS region at one time.

• Test will identify PWS in > 99% of cases and is used in some centers as a first line test for the molecular diagnosis of PWS. The advantage of MS-MLPA analysis over single locus DNA methylation analysis is that the MS-MLPA interrogates 5 separate differentially methylated sites. It can also

estimate the size and distinguish the deletion type (typical type I and II or atypical-larger or smaller than usual deletions in the 15q11-q13 region) [2, 6].

- Test can distinguish chromosomal deletion from uniparental disomy but cannot generally distinguish uniparental disomy from an imprinting defect, unless in rare individuals, a microdeletion of the imprinting center is seen.

- Test will not identify chromosomal rearrangements involving the proximal region of chromosome 15.

3.10.3. Fluorescence in-situ Hybridization (FISH) with High Resolution Karyotype

3.10.3.1. Description

- A venous blood sample from the proband must be collected for DNA extraction and isolation.

3.10.3.2. Normal Results

- A chromosomal analysis technique that permits cytogenetic localization of a DNA sequence to determine whether a chromosomal region or gene, has been deleted or rearranged.

- Fluorescently generated probe hybridizes and therefore generates a single fluorescent signal, at the PWS/AS region of chromosome 15q11-q13, indicating no deletions or rearrangements.

- Note that if prior DNA methylation analysis is positive and a "normal" FISH result is found, further testing to distinguish between uniparental disomy and an imprinting center defect is indicated.

3.10.3.3. Comments

- FISH tests are historically ordered as a follow up to positive results from DNA methylation analysis in order to further determine the PWS genetic subtype. It is done in conjunction with a karyotype study but current practice includes chromosomal or high resolution microarrays with SNP and CNV probes to determine the PWS genetic subtype.

- In the evaluation of PWS, a specific fluorescently labeled probe corresponding to the PWS/AS region (*e.g.*, SNRPN locus) may be utilized to identify deletions of the chromosome 15q11-q13 region.

- The combination of FISH with karyotype has historically distinguished chromosomal deletions from chromosomal rearrangements (translocations and in- versions) involving the 15q11-q13 region.

- FISH tests are not sensitive enough to be used as the first line molecular test to identify PWS and a negative FISH analysis does not exclude the diagnosis of PWS. Furthermore, FISH analysis alone will not identify the source (maternal or paternal) of the deletion in 15q11-q13 region (a paternal 15q11-q13 deletion is consistent with PWS while a maternal deletion is consistent with Angelman syndrome). Microarray testing is now considered to be an optimal test for determining PWS genetic subtypes, both postnatally and prenatally [23, 34].

- FISH test not discern among normal, uniparental disomy and imprinting center defects and requires living cells and chromosome testing for interpretation of results.

3.10.4. Chromosomal Microarray (CMA) or High-Resolution Microarray Using Single Nucleotide Polymorphism (SNP) and Copy Number Variant (CNV) Probes

3.10.4.1. Description

- Genetic testing technique utilizing chromosomal microarrays to detect deletion status [presence (and size) or absence] at the PWS critical chromosome region using copy number variant probes.

3.10.4.2. Normal Results

- Normal; High resolution microarrays using SNP probes can be used to identify Regions of Homozygosity (ROH) or areas within the genome having identical DNA patterns on chromosomes indicating consanguinity or large areas (*e.g.*, > 8Mb in size) with Loss of Heterozygosity (LOH) on specific chromosomes indicating uniparental disomy (*e.g.*, maternal disomy 15 in PWS), either contiguous or segmental. There are three maternal disomy 15 subclasses (*i.e.*, heterodisomy with no regions of homozygosity, segmental disomy or total isodisomy involving the entire chromosome 15 resulting from an error in female meiosis II) [23, 35, 60].

3.10.4.3. Comments

- Advantage of CMA or high-resolution microarray as compared to FISH includes query of the entire genome and therefore can provide information regarding deletions and duplications in the rest of the genome. Therefore, this test is useful when testing for PWS is negative.

- Disadvantage as compared to FISH is that microarrays will not identify chromosomal rearrangements (balanced translocations and inversions).

- SNP probes in the high-resolution microarray can assist in determining the maternal disomy subclass status (heterodisomy, total isodisomy or segmental isodisomy).

- CMA or high-resolution microarrays are more expensive than using FISH analysis but examines the entire chromosome complement using millions of probes and not only the study of a single chromosome as seen in FISH analysis.

- In the maternal isodisomy 15 subtype, the entire length to the chromosome 15 shows loss of heterozygosity with no evidence of DNA polymorphism. This indicates that the two maternal 15s are identical due to nondisjunction in gametogenesis or meiosis.

- In the maternal segmental isodisomy subtype, only segments of chromosome 15 show loss of heterozygosity (*e.g.*, > 8Mb in size). This indicates that both maternal 15s contain areas where crossing over occurred and genetic material was exchanged during the first stage of gametogenesis (in meiosis I) [3, 23, 35, 60].

- In the maternal heterodisomy 15 subtype, there is no evidence of loss of heterozygosity or crossing over in meiosis I. High resolution microarrays will not determine the PWS genetic subtype in this situation and additional genetic testing is needed such as genotyping with chromosome 15 DNA markers from the parents and PWS child.

3.10.5. Polymorphism Analysis of DNA Markers

3.10.5.1. Description

• A venous blood sample from the proband and both parents must be collected for DNA extraction and isolation.

3.10.5.2. Normal Results

• "Normal" result would indicate a pattern of polymorphisms in the proband indicating biparental or normal inheritance. In the context of a prior abnormal DNA methylation analysis, the molecular class would be an imprinting defect in the presence of proven paternity. A maternal-only inheritance pattern indicates maternal uniparental disomy.

3.10.5.3. Comments

• Genetic testing technique that compares the pattern of DNA marker polymorphisms of chromosome 15 loci among the proband and both parents to determine whether the inheritance pattern is biparental or maternal-only (maternal disomy).

• Test is typically ordered after DNA methylation test is consistent with PWS [62], but negative results are obtained from FISH analysis (*e.g*., no deletion). DNA polymorphism analysis aims to distinguish between maternal unipartental disomy and an imprinting center defect.

• Chromosome 15 DNA marker polymorphism analysis is not performed as a first line test, but is considered the "gold standard" test for defining uniparental disomy as the molecular class responsible for PWS but current studies indicate the value of identifying maternal disomy 15 by the use of high resolution microarrays with SNP probes [3, 5].

• If biparental (normal) inheritance is demonstrated, then further testing in a specialized laboratory is necessary to determine whether the imprinting defect is due to an epimutation or micro-deletion in the imprinting center.

3.10.6. DNA Sequence Analysis

3.10.6.1. Description

• A venous blood sample from the proband must be collected for DNA extraction and isolation. Current applications now use buccal cells or saliva for DNA isolation.

3.10.6.2. Normal Results

• "Normal" result would demonstrate a normal nucleotide sequence, with no mutations or deletions.

3.10.6.3. Comments

• Genetic testing technique that defines the Smallest Region of Overlap (SRO) for the PWS imprinting center.

• Test is reserved for rare situations after DNA methylation analysis (maternally methylated allele only), FISH (no deletion) and DNA polymorphism analysis (biparental inheritance) have been performed.

• DNA sequence analysis is performed in research laboratories.

• It is important to identify imprinting center microdeletions for genetic counselling purposes. The recurrence risk for additional children with PWS is impacted by whether the defect is due to a microdeletion or epimutation. If the father carries a microdeletion of the imprinting center on the maternally inherited chromosome 15, recurrence risk approaches 50%; if the defect is due to an epimutation, the recurrence risk is less than 1% [3].

3.11. Specific Clinic Testing

3.11.1. Adrenal Reserve Assessment

3.11.1.1. Description

Initial testing consists of measurement of the morning (8 AM) cortisol and ACTH level from a venous blood sample.

3.11.1.2. Normal Results

• 8 AM serum cortisol level ≥ 18 mcg/dl (500 nmol/L) indicates normal adrenal glucocorticoid production and secretion.

3.11.1.3. Comments

• Prevalence of central adrenal insufficiency (CAI) in individuals with PWS remains unknown [71, 72].

• Endocrine testing of the hypothalamic-pituitary adrenal axis to evaluate adequacy of glucocorticoid sufficiency has produced widely discrepant results [71-76]. There is no current gold standard in terms of the type of test used for adrenal insufficiency in PWS or the frequency of monitoring required. Most studies agree that some individuals with PWS have central adrenal insufficiency and so clinicians should not hesitate to treat with hydrocortisone if there is any clinical suspicion of possible adrenal insufficiency, even if only during times of illness or surgery [77].

3.11.2. Thyroid Function Tests

3.11.2.1. Description

• Measurement of serum thyroid stimulating hormone (TSH), free thyroxine (free T4) and free T3 levels from a randomly obtained venous blood sample.

3.11.2.2. Normal Results

• TSH: 0.5-4.5 mIU/L (age specific ranges may apply).

• Free T4: 0.7-2.0 ng/dL (age specific ranges may apply).

Free T3: 100-200 ng/dL.

3.11.2.3. Comments

• When interpreting test results, the reference interval supplied by the laboratory performing the test should always be used; these intervals are instrument and/or method-dependent. The nutritional supplement biotin can interfere with the assays for these levels, so individuals must be off of this supplement for one week before testing is done.

• A TSH level > 10 mIU/L combined with a free T4 level below the lower limit of the reference range is usually indicative of primary hypothyroidism.

• A TSH that is below the lower limit of the reference range or within the reference range combined with a low free T4 level may indicate central hypothyroidism.

• Borderline abnormal results should prompt repeat testing for confirmation.

• Assessment of thyroid function is advisable prior to initiating GH therapy, as well as periodically during treatment with GH.

3.11.3. Serum Insulin like Growth Factor 1 (IGF-1)

3.11.3.1. Description

• Randomly obtained venous blood sample, but IGF-1 levels are affected by fasting or fed state, so check on consistent nutritional state for each individual.

• IGF-1 is a hormone product synthesized and secreted by the liver in a non-pulsatile manner, in response to GH receptor stimulation.

• Serum IGF-1 levels are more stable in the blood throughout the day than GH, so it is a useful indicator of average GH levels.

• IGF-1 levels are altered by nutrition level, disease state, ethnicity, estrogen status, exercise status, stress, insulin levels and time of day. Therefore, it is recommended to also measure an IGFBP-3 level (the most abundant of the carrier proteins for IGF-1 in the blood) and calculate the molar ratio of IGF-1/IGFBP-3 to determine IGF-1 bioavailability.

• Children with PWS have elevated IGF-1 levels after 2 years of treatment with GH, but normal IGF-1/IGFBP-3 molar ratios which suggest that GH dose should be assessed using calculated bioavailable IGF-1 level rather than total IGF-1 level.

3.11.3.2. Normal results

• Normative ranges for age and sex are laboratory and assay dependent.

3.11.3.3. Comments

• An IGF-1 level < 0 SDS may indicate growth hormone deficiency. Infants or children with proven genetic diagnosis of PWS do not need provocative tests for GH secretion to confirm a diagnosis of growth hormone deficiency [2, 65].

3.11.4. Serum Fasting Glucose

3.11.4.1. Description

• Venous blood sample obtained following an 8-hour fast (no consumption of food or beverages other than water; usually overnight).

• If the result is abnormal, the test must be repeated to establish the diagnosis.

3.11.4.2. Normal Results

• 70-100 mg/dl (3.9-5.6 mmol/L).

3.11.4.3. Comments

• Current criteria for diagnosis of diabetes mellitus from the ADA include fasting plasma glucose level greater than or equal to 126 mg/dL (7 mmol/L).

• Current criteria for diagnosis of impaired fasting glucose from the ADA include fasting plasma glucose level greater than or equal to 100 mg/dL.

• Fasting glucose should be measured prior to commencing GH replacement therapy then every 6-12 months after maintenance doses are achieved [5].

3.11.5. Oral Glucose Tolerance Test

3.11.5.1. Description

• In the morning after a 10-hour fast the fasting plasma glucose level is obtained and a 75-g oral glucose load is then administered; periodic serum glucose measurement is then compared to an established nomogram for normal glucose metabolism, generally over a 2-hour period.

3.11.5.2. Normal Results

• Fasting serum glucose: 70-100 mg/dL.

• Serum glucose after 1 hour: < 200 mg/dL.

• Serum glucose after 2 hours: < 140 mg/dL.

3.11.5.3. Comments

• During the test, the patient should remain seated and should not smoke.

• Should be done only in patients whose diet and physical activity have been unrestricted for 3 days before testing.

• A plasma glucose level between 140 and 200 mg/dL at 2 hours after glucose load is considered due to impaired glucose tolerance (sometimes called "prediabetes"); this group is at increased risk for developing diabetes. A level greater than 200 mg/dL at 2 hours after glucose load is a sign of diabetes mellitus [2, 5, 24, 25].

• In the absence of unequivocal hyperglycemia, where the index of suspicion is high, repeat testing should be done.

3.11.6. Dual X-ray Absorptiometry (DXA) Scan

3.11.6.1. Description

• Imaging technique that measures Bone Mineral Density (BMD) (g/cm2) and can be used to measure body composition (fat and lean mass) [66].

• In pediatric and adolescents, measurement of BMD should occur at two sites- lumbar spine and total body BMD.

• Pediatric patients on GH therapy do not need routine DEXA scans, as GH normalizes bone mineral density during treatment.

• After age 11 years in girls and age 14 years in boys, bone mineral density should be assessed as it correlates with low sex hormone levels.

• Lean body mass has the strongest effect on bone mineral density, indicating that exercise in addition to GH therapy is important to optimize bone mineral density.

3.11.6.2. Normal Results

• Pediatric and adolescent BMD results are reported as Z-scores (mean values as compared to age-matched controls).

• Normal: A-Z score ranging from -2 to +2.

3.11.6.3. Comments

- DXA scans should be performed and interpreted by radiologists familiar with technical aspects of DXA scanning in pediatric and adolescent populations.
- Normative pediatric DXA datasets should be consulted, which take into account age, sex, ethnicity, weight and Tanner stage [2].

3.11.7. Polysomnography

3.11.7.1. Description

- Nocturnal laboratory-based diagnostic studies are used to assess for the presence of both central and obstructive sleep apnea; however, more hospitals now have the ability to perform home sleep studies, which give more accurate data of what is happening in home environment.
- Study quantifies the total time spent in sleep, time spent in sleep according to sleep stage, the number of arousals and hypoxemic events.
- Untreated or unrecognized gastroesophageal reflux disease can significantly affect the apnea-hypopnea index score as well as oxygen saturation levels. This needs to be evaluated in the event of severe obstructive sleep apnea-hypopnea discovered on polysomnography.

3.11.7.2. Normal Results

- The number (frequency) of apneic and hypopneic episodes per hour is used to determine the apnea/hypopnea index (AHI) or respiratory disturbance index (RDI) which includes respiratory-effort related arousals (RERA) from sleep that do not meet the definition of apneas or hypopneas although sleep is disrupted but does not disrupt sleep. They are characterized by increasing respiratory effort for 10 seconds or more leading to an arousal from sleep. A high RDI is significantly correlated with excessive daytime sleepiness. A normal result is an AHI or RDI of < 5 events hourly.
- Minimal oxygen desaturations should occur.

3.11.7.3. Comments

- Polysomnography is recommended prior to initiating GH therapy in individuals over age 2 years with PWS, as GH therapy can worsen obstructive sleep apnea in older children [2, 5, 24, 25].

Multiple Sleep Latency Test (MSLT) is a daytime sleep test that typically follows the overnight sleep study. It is used to determine whether daytime sleepiness is due to narcolepsy. It consists of several 20 minute nap opportunities set 2 hours apart during the day to assess the time elapsed until the person falls asleep and Rapid Eye Movement (REM) sleep is recorded. A sleep latency of less than 10 minutes is abnormal and less than 8 minutes together with onset of REM is indicative of narcolepsy.

- Tonsillectomy/adenoidectomy should be considered in individuals with moderate/severe obstructive sleep apnea on polysomnography.
- In the Global PWS Registry, fewer than 50% of individuals prescribed Continuous Positive Airway Pressure (CPAP) for sleep apnea used as prescribed or at all, so this may not be a good treatment option for much of the population.
- Infants with PWS typically have greater central sleep apnea than obstructive sleep apnea and this can be treated with supplemental oxygen or Bi-level Positive Airway Pressure (Bi-PAP).
- Narcolepsy is relatively common in individuals with PWS and should be evaluated using a Multiple Sleep Latency Test (MSLT) if there is suspicion of this diagnosis based on clinical reports.

3.11.8. Spine Radiographs

3.11.8.1. Description

- Posteroanterior and lateral radiographs of the spine, including the iliac crest and cervical spine, used to assess for scoliosis.

3.11.8.2. Normal Results

- No kyphosis, lordosis, or deformities.
- Proper alignment of the vertebral bodies.
- Cobb angle (coronal plane angle measurement) < 10 degrees.

3.11.8.3. Comments

- Adolescent scoliosis is identified by three-dimensional deformity of the spine with lateral curvature plus rotation of the vertebral bodies.
- Standing radiographs are usually sufficient for the initial evaluation of scoliosis. Right and left bending films usually are obtained only if the patient is being considered for bracing or surgery.
- Radiographs should be read and interpreted by radiologists or orthopedists with expertise in evaluating conditions of spinal curvature [2, 5, 24, 25].

3.12. Other Obesity-related Disorders

3.12.1. Section Content and Questions to Answer

The components are ordered by importance in bulleted format with common and key features that differ from PWS are described. How a disorder in the differential diagnosis can be differentiated from PWS will be discussed. Disorders in the differential diagnosis that present similarly to PWS but not linked by etiology, cause or effect, will be discussed. Names of diseases in the differential diagnosis will be discussed along with consultation advice for diagnostic dilemmas and procedures.

There are several imprinting disorders in humans that impact growth size and development due to errors in genomic imprinting besides PWS [51, 78]. These include:

3.12.1.1. Angelman Syndrome

- Complex imprinted disorder generally due to deletions of maternal chromosome 15q11-q13 region with loss of the UBE3A gene which is maternally expressed and under the control of a separate imprinting center within the region.

• Normal at birth with onset of symptoms at 6 months of age; characterized by microcephaly, gait ataxia, seizures, developmental delay, intellectual disability and behavioral disorder.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing, starting with DNA methylation testing showing the presence of only the paternal set of alleles.

3.12.1.2. Schaff-Yang Syndrome

• Syndrome similar to PWS due to disruption of expression of MAGEL2 gene on Ch 15.

• Symptoms include neonatal hypotonia, failure to thrive followed by hyperphagia, seizures, short stature, hypogonadism, developmental delay, intellectual disability, absent speech and sleep apnea. It is associated with joint contractures and autistic spectrum disorder.

3.12.1.3. Albright Hereditary Osteodystrophy

• Autosomal dominantly inherited condition of resistance to Parathyroid Hormone (PTH), resulting in hypocalcemia and hyperphosphatemia.

• Caused by inactivating mutations in the GNAS1 gene located on chromosome 20 [51].

• Characterized by developmental delay, round facies, short stature, obesity and short fourth metacarpal bones.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing and serum biochemistry (calcium, phosphorus, intact PTH levels).

3.12.1.4. Beckwith-Wiedemann Syndrome

• Overgrowth disorder caused by abnormally imprinted gene expression in the chromosome 11p15.5 region.

• The presentation is highly variable, characterized by macrosomia, visceromegaly, omphalocele and macroglossia.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing (Methylation specific-multiplex ligation probe analysis or MS-MLPA) [63, 64].

3.12.1.5. Silver-Russell Syndrome

• Inherited disorder due to epigenetic alterations involving the imprinting control region that regulates expression of the Insulin-like Growth Factor 2 (IGF2) gene or other genes located in the region of chromosome 11p15.5.

• Characterized by intrauterine or postnatal growth retardation and abnormal facies.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.6. Maternal Disomy 14

• Complex imprinted disorder with features similar to Prader-Willi syndrome, caused by maternal uniparental disomy of chromosome 14 or microdeletions of the 14q32.2 imprinted region.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.7. Spinal Muscular Atrophy

• Neonatal neuromuscular disorder caused by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem.

• Characterized clinically by hypotonia and weakness.

• Children usually die before the age of 1 year due to respiratory failure.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.8. Myotonic Dystrophy

• Autosomal dominantly inherited multisystem disorder caused by trinucleotide (DM1) or tetranucleotide (DM2) repeats.

• Numerous manifestations include skeletal muscle weakness, myotonia, muscle pain, cardiac conduction abnormalities, respiratory dysfunction and hypogonadism.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.9. Cohen Syndrome

• Autosomal dominant disorder caused by inactivating mutations in VPS13B gene.

• Characterized by developmental delay, intellectual disability, microcephaly and hypotonia.

• Abnormal facies are evident, with long eyelashes, downslanting eyes, bulbous nasal tip, a smooth or shortened area between the nose and the upper lip (philtrum) and prominent upper central teeth.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.10. Alström Syndrome

• Multisystem disorder that presents in infancy caused by mutations in ALMS1 gene on chromosome 2, possibly involved in cilia proteins.

• Characterized by dilated cardiomyopathy, obesity, type 2 diabetes mellitus, short stature and fibrosis of organs with shortened life expectancy.

• Progressive loss of vision and hearing with multiple organ involvement.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.11. Bardet-Biedl Syndrome

• Multisystem disorder that presents in childhood, caused by mutations of one of several genes encoding cilia proteins.

• Characterized by childhood obesity, retinitis pigmentosa, polydactyly, intellectual disability or learning problems and abnormal genitalia.

• Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.12. Fragile X Syndrome

- Form of inherited intellectual disability caused by inactivating mutations in the Fragile X Mental Retardation 1 (FMR1) gene, located on chromosome Xq27.3 and usually affects males.
- Characterized clinically by global developmental delay, intellectual disability and learning disabilities.
- Physical features include relative macrocephaly, blue irises, arched palate, joint laxity.
- Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.13. Single Gene Mutations (SIM1, POMC, MC4R)

- Monogenic disorders characterized by extreme obesity beginning in childhood.
- Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.14. Leptin Deficiency

- Congenital leptin deficiency is caused by mutations in the gene encoding leptin (LEP), whereas mutations in the leptin receptor (LEPR) causes leptin resistance.
- Massive obesity in early childhood, hyperphagia and delayed puberty due to hypogonadotropic hypogonadism are characteristic findings.
- Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.15. Cytogenetic Abnormalities Including Chromosomal Deletions of 1p36 or 16p11.2

- Microdeletions of either 1p36 or 16p11.2 cause intellectual disabilities and craniofacial abnormalities.
- The 1p36 deletion syndrome has multisystem effects, including congenital heart disease, renal, skeletal and ophthalmologic anomalies. Microcephaly, low set ears and flat nasal bridge are common.
- The 16p11.2 deletion syndrome is characterized by developmental delay/learning problems, dysmorphic features with digital anomalies, short stature and severe early-onset obesity.
- Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.16. Wilms' Tumor, Aniridia, Genitourinary Anomalies and Mental Retardation (WAGR) Syndrome

- Haploinsufficiency of the WT1 and PAX6 genes on ch11p13 to BDNF (11p14.1).
- Size of deletion determines degree of BDNF deficiency that in turn relates to obesity.
- Low birth weight; 100% obese by age 10 years; Wilm's tumor, aniridia, genitourinary anomalies, intellectual deficiency.
- Distinguished from Prader-Willi syndrome on the basis of molecular genetic testing.

3.12.1.17. Craniopharyngioma

- Craniopharyngioma and/or the consequences of treatment causing brain/hypothalamic damage can lead to features similar to those seen in Prader-Willi syndrome, particularly at an early age.
- This non-genetic condition is often referred to as "acquired Prader-Willi syndrome" or more recently as "hypothalamic obesity syndrome".
- Diagnosis is established through brain imaging and medical history of brain/hypothalamic tumor or damage.
- Unlike PWS where hyperphagia is associated with a satiety deficit, individuals with hypothalamic obesity have hunger that is insatiable.

3.12.1.18. Early onset Morbid Obesity

- Presence of obesity, hyperphagia and large body size. These individuals can be large at birth and continue to be larger than their peers throughout childhood and into adulthood.
- Greater degree of developmental delay, intellectual impairment and behavioral problems than in Prader-Willi syndrome.
- Other causes of obesity including obesity-related syndromes should be ruled out including Prader-Willi syndrome and other related over-growth or obesity disorders.

3.12.1.19. Syndrome Summaries

- Several of these disorders can resemble PWS, specifically obesity and learning/behavioral problems. If the DNA methylation test is normal (not indicative of PWS), then these clinical disorders may be considered to account for the clinical presentation.
- During infancy, other chromosome rearrangements, infections, metabolic derangements (*e.g*., mitochondrial defects), spinal muscular atrophy, myotonic dystrophy or brain insults or anomalies should be considered. Later, other obesity-related conditions (*e.g*., Cohen, Alström, Bardet-Biedl, fragile X) should be considered as well as single gene mutations (*e.g*., SIM1, POMC, MC4R) [79-81], leptin deficiency or other cytogenetic abnormalities (*e.g*., 1p36 or 16p11.2 deletions) [82].

Additional cytogenetic abnormalities reported in individuals with obesity and learning /behavioral problems resembling PWS are duplications (3p25.3-p26.2 and Xq27.2-qter), but more commonly deletions of chromosome regions 1p36, 2q37.3, 6q16.2, 10q26, 11p12-p14, 16p11.2, 20q13.13-q13.32 or Xq26.3 [82]. Besides obesity, many of these cytogenetic or single gene disorders will present with birth defects or other clinical information that are not commonly seen in PWS and should help distinguish them from PWS. These include overgrowth and an omphalocele in Beckwith-Weidemann syndrome, a family history of male mental retardation in fragile X syndrome or retinitis pigmentosa in Bardet-Biedl syndrome.

- Genome-wide and sequencing studies and microarray analysis have identified at least 60 gene loci or defects associated with an obesity phenotype including FTO, POMC, SH2B1, MC4R, TUB and BDNF genes. Several of these

genes are known to contribute individually or collectively to extreme childhood obesity, increased body mass index, waist circumference or waist-to-hip ratios and if recognized early, can be treated to avoid the health-related complications in individuals carrying these genetic defects. At least 370 genes have currently been recognized in playing a role in human obesity [83].

• *Craniopharygioma* and/or the consequences of treatment causing brain/hypothalamic damage can lead to features similar to those seen in PWS, particularly at an early age. This non-genetic condition is often referred to as "acquired Prader-Willi syndrome" or "hypothalamic obesity syndrome" [2].

3.13. Consultation for Diagnosis

3.13.1. Section Content and Questions to Answer

Consultation for diagnostic dilemmas and procedures are described in bulleted format and outlined.

3.13.1.1. Introduction and Background

A trained medical geneticist, usually a board certified clinical geneticist will be involved with the diagnosis and care throughout the patient's life time specifically to order appropriate genetic testing to confirm the diagnosis of PWS and interpret results. They will supply information about the syndrome and treatment options including providing genetic counseling services for family members.

3.14. Treatment and Medications

3.14.1. Section Content and Questions to Answer

The overall treatment approach will be summarized including medication and non-drug modalities that are concordant with their coverage in sections below followed in bulleted format.

3.14.1.1. Introduction and Background

• There is a paucity of evidence-based data supporting the use of medical approaches documented for PWS; however, standard recommendations for treatment have been published by professional societies and published reviews or textbooks [2, 5, 6, 24, 25, 84-87].

• Treatment of PWS involves the management of several co-morbidities that constitute the syndrome and the ongoing assessment for the emergence of associated conditions and complications that evolve over the lifespan of an individual with PWS.

• As with individuals without PWS, the role of pharmacogenetics and individual drug metabolism rates can influence the effect of the medication on treatment.

3.14.2. Medication Use

• No single medication is available to treat or cure this genetic disorder.

• Replacement for growth hormone, sex steroids, thyroid hormone and glucocorticoids are indicated if and when deficiencies arise.

• Medications are also used to treat behavioral problems, if behavioral management therapy is unsuccessful. The use of pharmacogenomic testing is becoming more common in clinical practice to check the status of the Cytochrome (CYP) p450 hepatic enzyme system encoded by specific genes required for normal drug metabolism. Alternations in these genes can significantly affect selection of medication types and dosage [88-90].

• Medications can be helpful to manage the obesity-related complications associated with PWS, but to date, there is no medication that has successfully managed the drive for food acquisition. Although, depending on the pharmacogenomic testing, weight gain is noted in those with or without PWS when prescribed certain atypical antipsychotics (*e.g.*, risperidone), if the drug metabolism or neurotransmitter receptor functions are altered.

3.14.3. Failure to Thrive

• Assisted feeding techniques are often required for infants with poor suck.

• During infancy, the goal is to maintain weight between the 25th through 75th percentile using established syndrome specific growth charts for PWS [68]. A recommended diet consists of the following macronutrient percentages: 25-30% protein, 30-40% carbohydrate and 25-30% fat. Increased dietary protein allows for increased muscle mass to occur when growth hormone is prescribed for PWS infants and children as well as to improve stature. Many parents overly restrict carbohydrate or fat intake in an attempt to prevent obesity, but it must be stressed that a well-balanced diet is critical for individuals with PWS. Overall, the caloric intake needs should be monitored closely to avoid obesity in childhood and in a food secure environment to avoid the failure to thrive in PWS infants [2, 5, 26, 84, 85].

3.14.4. Overweight/Obesity

• Weight management is one of the most important aspects of treatment along with endocrine disturbances for individuals with PWS. Specific dietary guidelines and development of clinical trials are underway or have been established with the goal of appetite treatment preventing obesity, skin picking and related complications [2, 5, 27, 84, 85, 91-96].

3.14.5. Endocrine

• Endocrine problems due to dysregulation of the hypothalamic-pituitary axis are common in PWS. A recommended initial consultation is warranted with a pediatric endocrinologist at diagnosis, including for thyroid and adrenal function (particularly during times of stress) and for growth. These endocrine concerns should be also be monitored with periodic hormone surveillance (*e.g.*, every 6 months during infancy and yearly at later ages) [5, 24, 25, 86, 87, 91, 92]. Premature adrenarche is common and requires no treatment other than reassurance. Premature puberty is uncommon and will require treatment with gonadotropin suppressants until age-appropriate puberty.

• Growth hormone insufficiency is considered a nearly universal finding in PWS; therefore, provocative testing is generally not required before growth hormone therapy. Growth hormone is used successfully for treating infants as

early as 2 months of age once the diagnosis of PWS is genetically confirmed.

• *Hypogonadism* is present in both males and females and has both a primary and central (hypothalamic) etiology, with the latter believed to be more influential. Although individuals with PWS do enter puberty, the progress is arrested and puberty is not complete. *Testosterone* (in males) and estrogen (in females) treatment should be considered as recommended by the endocrinologist in discussion with the parents, depending on the age of the patient, their history of mood instability and aggressive behavior [2, 5, 86].

3.14.6. Scoliosis, Risk for Fractures and Other Orthopedic Problems

• *Scoliosis* is seen in about 40% of individuals with PWS ranging from mild to severe and may worsen during growth hormone treatment. It should be monitored closely with scoliosis related x-ray series first obtained at 18 months of age when the patient with PWS is treated with growth hormone in early infancy as a baseline along with bone density and bone age studies and orthopedic consultations, if scoliosis is suspected [1]. Bracing and scoliosis surgery may be required. Scoliosis is not affected by PWS genetic subtypes but those with higher weights or BMI may develop kyphotic deformities with scoliosis and are at a higher risk for surgical intervention. Associated limb malalignment is also more common in PWS when scoliosis occurs and often includes foot abnormalities. Growth hormone treatment for stature commonly prescribed in PWS infants, children and adolescents should have growth rate followed closely and monitored for spinal curvature and signs of scoliosis. Growth hormone can improve bone density, muscle mass and strength as well which also would improve surgical outcomes, if surgery is needed [2]. There are more surgical complications for those with PWS due to their hypotonia, decreased muscle mass and strength, osteoporosis, narrow airway and self-injury with skin picking at the incision sites, common in this disorder.

• *Osteoporosis* and *osteopenia* commonly develop in PWS and bone mineral density should be monitored with DXA scans [66].

• Calcium and vitamin D supplements should be considered to optimize attainment of peak bone mass. The use of weight bearing exercises is often advised [2, 5, 24, 25].

3.14.7. Psychiatric and Behavioral Problems

3.14.7.1. Description

• Many behavioral problems in PWS can be attributed to food insecurity. Food insecurity increases anxiety and preoccupation with potential food sources, which in turn triggers food seeking. The fundamental approach to behavioral management in PWS is the establishment of an environment that provides controlled or supervised food access and psychological food security. Food security means the person with PWS understands their daily menu (food and portion size), knows the time of day when meals and snacks will be served and realizes that there is no opportunity for acquiring unauthorized food. A daily plan that is organized as a visual, linear schedule that alternates preferred (leisure skills) with non-preferred activities (exercise, work and sensory motor stimulation) will decrease anticipatory anxiety, noncompliance and improve transitions throughout the day.

• Behavioral management and counseling programs are an important component of treatment for individuals with PWS. Active partnership and participation of the parents, teachers, primary care provider, pediatrician and psychologist are required. Behavior management works best by rewarding desired behaviors, giving low attention to undesirable behaviors, providing incentives and outlining consequences of inappropriate behavior [2].

• A consistent, predictable and safe environment should be established for all persons with PWS. The person with anxiety or anger management problems may require modifications to standard psychological treatment with cognitive behavioral therapy, applied behavioral analysis and social skills training. Building adaptive coping strategies should be accomplished through coaching (scripted, rehearsed and cued interventions). The person with PWS is unlikely to initiate or carry out these interventions autonomously.

• Psychotropic medications are used to treat co-morbid psychiatric disorders that occur in PWS or to help in the management of phenotypic behaviors. Medications that have been used occasionally to treat behavior problems include stimulants, alpha-adrenergic agonists, beta blockers, mood stabilizers (lithium, valproate, lamotrigine), typical and atypical antipsychotics and antidepressants, specifically Selective Serotonin Reuptake Inhibitors (SSRIs). These classes of medications have been used to treat the emotional disturbances, depression, impulsivity, aggression, obsessive-compulsive tendencies and psychosis occurring in patients with Prader-Willi syndrome, but no selection or order of medications has been approved specifically for treating behavioral problems in PWS, as the response may vary from patient to patient [2].

• Individuals with PWS are stress sensitive and susceptible to anxiety and depression. Although the risk of psychosis is increased among all genetic subtypes in PWS, the maternal disomy 15 form of PWS has been associated with bipolar disorder and cyclic psychosis that appears to increase with age beginning in adolescence.

• Catatonia has occurred in young adults with PWS in association with psychosis, mood disorders, medical illness or seizures. It is a psychomotor syndrome characterized by muscular rigidity (less evident in PWS), waxy flexibility, echolalia or mutism, negativism or excited delirium. The onset of symptoms progresses rapidly over 24-72 hours requiring emergency medical evaluation and treatment. It has been associated with low serum iron. Catatonia responds to lorazepam, but when symptoms persist Electroconvulsive Therapy (ECT) is required. Without treatment, catatonia can become malignant with symptoms of muscle breakdown indicated by elevations in creatinine phosphokinase, similar to neuroleptic malignant syndrome. The etiology of catatonia involves loss of GABA tone in the central nervous system. Genetic loci for periodic catatonia map to chromosome 15q15 just outside the PWS region.

• Although haloperidol was used extensively in the past for management of the behavioral as well as psychotic symptoms in persons with PWS, the atypical antipsychotic agents

are now used almost exclusively. These include risperidone, aripiprazole, quetiapine and ziprasidone. There is international consensus for the use of risperidone for psychosis and impulsive aggression.

• Antipsychotic medications may be prescribed for psychotic symptoms including delusions and hallucinations, but they can have side effects. The typical extrapyramidal side effects of tremors, stiffness or cogwheeling may not be as evident in persons with PWS due to syndromal hypotonia. Loss of facial expression, arms hanging without associated arm swing and shuffling gait are the best indicators of extrapyramidal side effects and need to be monitored closely in PWS. Individuals with PWS are at the same risk as the general population for tardive dyskinesia. Also, neuroleptic malignant syndrome has occurred, but identification of symptoms may be delayed because of hypotonia, decreased muscle mass, temperature dysregulation and pre-existing signs of dysautonomia in PWS. Weight gain associated with the use of atypical neuroleptics is reported in PWS but less likely than in the typical population when food is managed by controlled access. Persons with PWS who are receiving antipsychotic medications may also be at-risk for iatrogenic hypothermia [2].

• The antianxiety agents, such as benzodiazepines and buspirone, may help with anxiety, rigid egocentric thinking and insomnia but can produce sedation and decreased mental alertness [2]. Benzodiazepines can also suppress respiration.

• Some medications can produce iatrogenic mood and behavioral activation in PWS. These include SSRI's, NSSRI's, aripiprazole, modafanil, gonadal steroids and rarely stimulants or alpha-adrenergic agonists. Symptoms include increased intensity of phenotypic behaviors, followed by increased impulsivity, mood lability and possibly psychosis [2].

3.14.8. Medications and Hormone Replacement

3.14.8.1. Description

For each medication, subsections on indications, dose and related information (*e.g.*, route and frequency and duration of administration), major contraindications and comments will be presented and limited to those of greatest clinical relevance. Evidence Based Medicine (EBM) entries and appropriate information will be summarized and effectiveness of various regimens discussed in bulleted format and described accordingly.

3.14.8.2. Hormone Replacement

Recombinant human Growth Hormone (rhGH).

3.14.8.3. Indications

• Treatment of growth failure in PWS [65].

• Treatment with growth hormone can improve body composition and physical strength, as well as motor and mental development [74].

• Growth hormone treatment improves the phenotype of both children and adults with PWS with or without the presence of growth hormone deficiency.

3.14.8.4. Dose and Related Information

• Starting dose: 0.5 mg/m2 /d administered SQ once daily beginning at or before age 2 years; alternative dosage of 0.24 mg/kg/wk.

• Only available in subcutaneous formulation.

• Major contraindications: active malignancy; severe obesity (weight >225 percent of ideal body weight; severe respiratory impairment.

3.14.8.5. Comments

• Children with PWS and clinically significant obstructive airway disease or apnea, gastroesophageal reflux with poor airway protection, morbid obesity or uncontrolled weight gain should receive attention to and/or treatment of these medical issues prior to commencement of GH therapy.

• Provocative testing to demonstrate GH deficiency is unnecessary for patients with genetically confirmed PWS who demonstrate growth failure.

• Titrate dose (usually about 1.0 mg/m2/d) in PWS infants to achieve insulin like growth factor 1 (IGF-1) levels in the upper one- half of the normative range for age for infants and children.

• Monitor for clinical effects that would indicate over- replacement, such as sleep apnea, edema, worsening/new snoring, headache, excessive long bone growth worsening of scoliosis.

• rhGH is FDA-approved for use in PWS beginning at age 2 years, but now commonly used at an early age (by 2-3 months) and has shown beneficial effects on motor development, muscle and cognition. It is in common use in this patient population. Head circumference increases can be related to skull bone thickening [5].

• Continuation of treatment into adulthood after epiphyseal closure to sustain the beneficial effects of rhGH on body composition and bone mass is controversial. If used, the transition from pediatric to adult use of rhGH should be guided by endocrinologists.

3.14.8.6. Evidence

• A meta-analysis studying the effect of rhGH therapy on body composition in adults with PWS identified 8 studies that included 134 individuals treated with rhGH for 12 months. Treatment of individuals with PWS with rhGH led to [weighted mean difference (MD) 95% confidence interval (CI)] reduced body fat (MD: -2.9%; CI: -3.90 to -1.910), visceral fat (MD: - 32.97cm^2; CI: -55.67 to -10.26), subcutaneous adiposity (MD: -55.24 cm^2; CI: -89.05 to -21.22) and increased lean body mass (MD: 2.41 kg; CI: 1.32 to 3.49). Studies of longer duration confirmed the findings for change in body fat (MD: -2.89%, CI: -4.69 to -1.07) and lean body mass (MD: 2.82 kg; CI: 1.31 to 4.33). Individuals treated with rhGH for 12 months did exhibit small increases in fasting glucose (MD: 0.27 mmol/L; 95% CI: 0.05 to 0.49) [87].

• A multicenter prospective trial studied the effects of long-term continuous rhGH treatment on body com- position, growth, bone maturation and safety parameters in

children with PWS. 55 prepubertal children (mean age of 5.9 ± 3.2 years) were followed over 4 years while treated with rhGH (1.0 mg/m2). Body fat percentage (SDS) was significantly lower after 4 years of rhGH treatment ($P < 0.0001$). Lean body mass SDS significantly increased during the first year of treatment ($P = 0.02$) but returned to baseline values the second year and remained unchanged thereafter. Mean ± SD height normalized from -2.27 ± 1.2 SDS to -0.24 ± 1.2 SDS ($P < 0.0001$) after treatment with rhGH. Body mass index SDS significantly decreased. Thus, body composition and height were significantly improved in children with PWS after long-term treatment with rhGH. No adverse effects were noted on bone maturation, blood pressure, glucose homeostasis and serum lipids [91].

• A Randomized Controlled Trial (RCT) studied the effects of rhGH treatment on cognitive functioning in 50 prepubertal children (ages 3.5 to 14 yr) with PWS. Cognitive functioning was measured biennially by validated intelligence tests [the Wechsler Preschool and Primary Scale of Intelligence-Revised, Dutch version (WPPSI-R) or the Wechsler Intelligence Scale for Children-Revised, Dutch version (WISC-R)]. Total intelligence quotient (IQ) score was estimated based on two subtest scores. After 4 years of GH treatment, mean Standard Deviation Scores (SDS) on the Similarities and Block design subtests were significantly higher than at baseline [mean difference (MD); 95% confidence interval (CI)] for Similarities test- MD: +0.4; 95% CI: -0.1 to 0.7; $P = 0.01$ for Block Design- MD: +0.3; CI: 0.07 to 0.6, $P = 0.01$. These results indicate that long-term GH treatment significantly improves abstract verbal reasoning and visuospatial skills and reduces the gap between children with PWS and healthy controls on these skills. Thus, during long-term GH treatment, children with PWS developed their vocabulary at the same pace as healthy references. The mean estimated total IQ score improved 4 points during 4 years of GH treatment, but this result did not reach significance ($P = 0.2$) [92]. A more recent review of growth hormone treatment protocols in PWS was summarized by Deal, C., Tony, M., Hoybye, C. and the 2011 GH in PWS Clinical Care Guidelines Workshop Participants. Growth Hormone Research Society workshop summary: Consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome [65]. This reference is important for health care providers treating PWS infants, children and adults with GH.

3.14.9. Testosterone

3.14.9.1. Indications

Treatment of hypogonadism and induction of puberty in males with PWS; prevention of osteoporosis [5].

3.14.9.2. Dose and Related Information

• Starting dose in early adolescence: either as 50 mg IM once a month, beginning around age 14; may increase by 25-50 mg every 6 months as needed or applied *via* transdermal patch or gel preparation.

• FDA approved as an intramuscular injection for children and adults, but available in transdermal and gel preparations for adults.

• Major contraindications: prostate or male breast cancer (adults).

3.14.9.3. Comments

• Establish a baseline on behavior before starting medication, as parents have reported increased aggression concurrent with testosterone treatment, although evidence based studies do not support this finding [97].

• Initiate low dose therapy and titrate cautiously, assessing behavior before each dose change to avert any undesirable effects.

• Establish minimal effective dose that will achieve clinical and biochemical eugonadism.

• Systematic studies evaluating the benefits and safety of sex hormone replacement in adolescents or adults with PWS are not available.

• Monitor testosterone level annually to target dosing (once eugonadism is achieved) and monitor hemoglobin periodically for development of polycythemia.

• Monitor for new or worsening glucose intolerance and/or worsening of scoliosis.

• Protects against osteopenia/osteoporosis.

3.14.10. Estradiol

3.14.10.1. Indications

• Treatment of hypogonadism and induction of puberty in females with PWS; prevention of osteoporosis [5].

3.14.10.2. Dose and Related Information

• Dosing is recommended based on Turner syndrome protocol to achieve maximum growth [98, 99]. Start with 0.1 μg/kg, by cutting an estradiol patch and applying at night and remove in the morning. After 6 months, continue 0.1 μg/kg continuously (change patch as directed). At 12 months after initiation of treatment, can increase dosing to 0.2 μg/kg. When breakthrough bleeding occurs, start progestin (5 mg oral medroxyprogresterone for 12 days/month) or change to oral contraceptive pills.

• Starting dose: 0.25 mg micronized PO daily beginning at around age 12 years.

• Transdermal starting dose: 14 mcg transdermal daily but usually applied twice weekly.

• Major contraindications: Vaginal cancer, cervical cancer, uterine cancer or other estrogen-responsive tumors; undiagnosed vaginal bleeding; pregnancy.

• Mood and behavior problems can occur as a result of estradiol therapy. Assess mood and behavior at baseline and during titration.

3.14.10.3. Comments

• Often females with PWS never develop menses due to sex hormone deficiency throughout life, although some acquire their periods spontaneously in their mid 20's.

• Starting dose of estradiol is not sufficient to induce menstruation. After initiation, increase the dose of estradiol gradually over a two year time span to achieve the adult dose of 2-4 mg micronized PO daily (or 100-200 mcg transdermal daily).

• After two years, or once breakthrough bleeding occurs on unopposed estradiol, add cyclic progestin (or replace estradiol with a low dose oral contraceptive that contains both estrogen and progesterone).

• Systematic studies evaluating the benefits and safety of sex hormone replacement in adolescents or adults with PWS are not available. Similarly longitudinal studies on continuation of sex hormone replacement in females with PWS throughout life are not available.

• The hypogonadism in PWS is a manifestation of both central and gonadal insufficiency and the extent of each varies across development from person to person. The have been a few pregnancies among PWS women. The onset of menses does not automatically indicate fertility. Assessment of estradiol, gonadotropin hormones and inhibin B (levels greater than 20 pg/ml indicate potential fertility) are necessary. Inquiry about sexual behaviors is recommended with a discussion of birth control if indicated [100].

• Protects against osteopenia/osteoporosis.

3.14.11. Micronized Progestin

3.14.11.1. Indications

• Treatment of hypogonadism in females with PWS (in combination with estradiol).

3.14.11.2. Dose and Related Information

• Starting dose: 200 mg PO days 1 to 12 of the calendar month.

3.14.11.3. Major Contraindications

• Vaginal cancer, cervical cancer, or uterine cancer; undiagnosed vaginal bleeding; history of thrombophlebitis or thromboembolic disease.

3.14.11.4. Comments

• The addition of a progestin to the sex steroid replacement regimen is advisable after estradiol therapy has begun to prevent endometrial hyperplasia, usually 2 years after estradiol treatment begins.

3.14.12. Psychotropic Medications

3.14.12.1. Description

• Psychotropic medications may be prescribed to augment the efficacy of behavioral interventions, to target situational disturbances and/or to treat symptoms of psychiatric disorder in individuals with PWS. A common practice in PWS is to begin the medication at a low dose and adjust upward with caution when indicated. A pediatrician or primary care physician will be comfortable prescribing stimulant and antidepressant medication, but psychiatric consultation and treatment may be needed if the patient does not respond as expected, if side effects occur or if signs of major psychiatric disorder are present. Psychiatric diagnosis always informs treatment. Genetic testing of the Cytochrome (CYP) p450 hepatic enzyme gene network is a new field in medical practice which is related to personalized medicine. The study of polymorphisms or variants impacting function of genes involved with drug metabolism will impact drug selection and dosage per individual. It is now becoming an active area of investigation with application in the clinical setting. This should be considered prior to prescribing psychotropic medications and/or in those individuals not successfully treated with routine medication and dosage protocols [89, 90]. The level of obesity, gastric emptying and intestinal absorption may also impact response to medication. There are very few double-blind placebo- controlled trials of psychotropic medications in PWS.

3.14.13. Stimulant Medications

3.14.13.1. Indications

• Treatment of symptoms of Attention Deficit Hyperactive Disorder (ADHD), excessive daytime sleepiness, or narcolepsy.

• Baseline behavioral assessments are usually obtained from the school or workplace. Standardized tools include the Connors Rating Scales, the Vanderbilt Assessment Scales and the Clinical Attention Problem scale (CAP) rating scale. These tools are also used to monitor treatment response. Affected children with PWS are more likely to have attention problems without hyperactivity.

3.14.13.2. Dose and Related Information

• Starting doses of methylphenidate or dextroamphetamine medication are determined by body weight (0.3-1.5 mg/kg) in childhood.

• During each visit, blood pressure, pulse and body weight should be obtained, even though appetite suppression with weight loss is rarely observed in persons with PWS treated with stimulant medications.

• Stimulants are well tolerated, but may be associated with elevated blood pressure, palpitations, irritability and insomnia. They may lower the seizure threshold. Side effects are minor and may include dry mouth, constipation, headache, stomachache (a rare complaint in persons with PWS) and skin rash.

• The typical response rate for symptoms of ADHD with stimulant medication is 75% and a person responding to one stimulant is likely to respond to another. The selection of an agent is often determined by clinician familiarity and side effects emerging with treatment. There may be a preference for dextroamphetamine in persons with PWS because it has a weak antianxiety effect due to monoamine oxidase inhibition.

It is best to start with short acting medications, such as:

• Methylphenidate: Ritalin (5, 10, 20 mg tablets); 2-5 hours.

• Dexmethylphenidate: Focalin (2.5, 5, 10 mg tablets); 2-5 hours.

• Dextroamphetamine: Dexedrine (5, 10 mg tablets); 4-6 hours.

• Mixed amphetamine salts: Adderall (5, 7.5, 10, 12.5, 15, 20, 30 mg tablets); 4-6 hours.

Once an optimal dose of response and efficacy has been established, then a dose equivalent of sustained or continuous release agent can be tried, such as:

• Methylphenidate sustained release: Ritalin SR (20 mg); 6-8 hours.

• Methylphenidate extended release: Concerta (18, 27, 36, 54 mg tablets up to 72mg); Metadate CD (10, 20, 30, 40, 50, 60 mg capsules up to 60mg); Ritalin LA (10, 20, 30, 40 mg capsules); 8-12 hours.

• Dexmethylphenidate delayed action: Focalin XR (5, 10, 15, 20 mg capsules); 5-8 hours.

• Dextroamphetamine sustained release: Dexedrine spansule (5, 10, 15 mg capsules); 6-8 hours.

• Mixed amphetamine salts extended release (Adderall XR) (5, 10, 15, 20, 25, 30 mg capsules); 8-10 hours.

• Mixed amphetamine salts extended release: Mydayis (25, 50 mg capsules); 12 hours.

• Lisdexamfetamine (Vyvanse) (20, 30, 40, 50, 60, 70mg capsules); 12 hours.

3.14.13.3. Major Contraindications

• Cardiac abnormalities or abnormal rhythm may require cardiology evaluation before initiating treatment.

• Drug-drug interactions occur with decongestants such as phenylephrine, phenylpropanolamine and pseudoephedrine producing elevated blood pressure and confusion.

• Occasionally typical doses of stimulants can produce mood and behavioral activation in children and adolescents with PWS. This may respond to dose reduction.

3.14.13.4. Comments

• Monitor for increased heart rate and blood pressure. Stimulants are controlled medications that carry a risk for tolerance or abuse.

• Appetite suppression and weight loss are not observed in children or adolescents with PWS.

3.14.14. Non-stimulant Medications

3.14.14.1. Indications

• Treatment of symptoms of Attention Deficit Hyperactive Disorder (ADHD), disruptive behavior associated with hyperarousal and anxiety.

3.14.14.2. Dose and Related Information

• Atomoxetine (Strattera) norepinephrine reuptake inhibitor (0.5mg/kg/d-1.2mg/kg/d).

• Alpha adrenergic agonists (short acting): Guanfacine (0.5mg-1mg TID); Clonidine (0.05mg-0.1mg TID).

• Alpha adrenergic agonists (long acting); Guanfacine ER (1-4 mg per day); Clonidine ER (Kapvay) (0.1-0.2 mg 1-2 times per day).

3.14.14.3. Comments

• May produce sedation. A decrease in hyperarousal and hyperactivity may be seen soon after initiating therapy, but it may take weeks to months to decrease achieve anxiolytic effects.

• Monitor blood pressure and pulse.

3.14.15. Other Non-stimulant Medications

3.14.15.1. Indications

• Treatment of excessive daytime sleepiness and narcolepsy.

3.14.15.2. Dose and related information

• Modafanil (Provigil) (100-400 mg q am); may increase dose and administer up to twice daily, if needed.

• Armodafanil (Nuvigil) (50-250 mg q am).

3.14.15.3. Comments

• Watch for mood and behavioral activation, headache and insomnia.

3.14.16. Selective Serotonin Reuptake Inhibitors (SSRIs)

3.14.16.1. Indications

• Treatment of anxiety, depression, obsessive/compulsive tendencies and cognitive rigidity in PWS [2, 25].

3.14.16.2. Dose and Related Information

Because mood and behavioral activation have occurred at typical starting doses of SSRI medications, it is recommended to start at half dose and titrate more slowly:

• Fluoxetine: Prozac (10 mg scored tablet; 20, 40 mg capsules) initially, 5 mg/d orally; increase at intervals of no shorter than 4 weeks.

• Paroxetine: Paxil (10, 20, 30, 40 mg tablets) initially 5 mg/d orally; increase at intervals of no shorter than 2 weeks.

• Sertraline: Zoloft (25 mg scored tablet; 50, 100 mg tablet) initially 12.5 mg/d orally; increase at intervals of no shorter than 2 weeks.

• Fluvoxamine: Luvox (25, 50, 100, 150 mg) initially 12.5mg/d orally; increase at weekly intervals up to 50 mg, then divide into 2 daily doses.

• Citalopram: Celexa (10, 20, 40 mg tablet) initially 5 mg/d orally; increase at intervals of no shorter than 2 weeks.

• Escitalopram: Lexapro (5 mg; 10, 20 mg scored tablets) initially 2.5mg/d orally; increase at intervals of no shorter than 2 weeks.

3.14.16.3. Major Contraindications

• Concurrent use of Monoamine Oxidase Inhibitors (MAOIs).

3.14.16.4. Comments

• FDA reports increased awareness (FDA black box warning) of the risk of suicidal ideation and behavior after starting SSRI medications. The risk of increased self-harm must be weighed against the efficacy of reducing target symptoms.

• Use caution in patients with hepatic or renal impairment; a dose reduction may be necessary.

• Systematic studies evaluating the benefits and safety of SSRIs in children, adolescents or adults with PWS are not available.

• FDA reports a warning related to Celexa (citalopram) because of the risk of dose-related QT prolongation. ECG monitoring and/or electrolyte monitoring should be performed if citalopram is used.

3.14.17. Selective Serotonin and Norepinephrine Reuptake Inhibitors (SSNRIs)

3.14.17.1. Indications

Treatment of anxiety and refractory depression in adolescents.

3.14.17.2. Dose and Related Information

Because mood and behavioral activation have occurred at typical starting doses of SSNRI medications, it is recommended to start at half dose and titrate more slowly:

• Venlafaxine HCl (Effexor) (25, 50, 75, 100, 225 mg tablets) 2-3 doses per day; increase at interval of one week.

• Venlafaxine HCl XR (Effexor XR) (37.5, 150, 225 mg capsules) 1-2 doses per day; increase at interval of 2 weeks.

• Desvenlafaxine HCl extended release (Pristiq) (25, 50 mg tablets) 1 dose per day; increase at interval of 2 weeks.

• Duloxetine (Cymbalta) (20, 30, 40, 60 mg capsules) 1 capsule twice daily; increase at an interval of 2 weeks.

3.14.17.3. Major Contraindications

• Concurrent use of Monoamine Oxidase Inhibitors (MAOIs).

• Anticholinergic side effects of dizziness, constipation, rapid pulse, sedation.

3.14.17.4. Comments

• FDA reports increased awareness (FDA black box warning) of the risk of suicidal ideation and behavior after starting these medications. The risk of increased self-harm must be weighed against the efficacy of reducing target symptoms.

• As with the SSRIs, mood and behavioral activation is dose related.

• Use caution in patients with hepatic or renal impairment; a dose reduction may be necessary.

3.14.18. Other Antidepressants

3.14.18.1. Indications

• Treatment of ADHD, daytime sleepiness, depression and refractory depression:

3.14.18.2. Dose and Related Information

• Bupropion HCl (Wellbutrin) (100-450 mg per day) in 3 divided doses; increase at interval of one week.

• Bupropion HCl sustained release (Wellbutrin SR) (150-450 mg per day) in 2 divided doses; increase at interval of 2 weeks.

3.14.18.3. Major Contraindications

• May lower the seizure thresh-hold.

Treatment of difficulty, falling asleep and staying asleep.

3.14.18.4. Dose and Related Information

• Trazadone (Desyrel) (50, 100, 150, 300 mg scored tablets) take at hour of sleep; increase dose by 50 mg weekly.

• Doxepin (Sinequan) (10, 25, 50, 75, 100 mg capsules) 10-30 mg at hour of sleep, increase daily as needed. Not approved for use in children <18 years, but highly effective for sleep induction and as an antihistamine for itching of the skin at nighttime.

3.14.18.5. Comments

• FDA reports prolonged QT interval with higher doses of trazadone; priapism has also been reported.

• Use caution in patients with hepatic or renal impairment; a dose reduction may be necessary.

• Anticholinergic effects include dry mouth, urinary retention and may exacerbate constipation.

3.14.19. Antianxiety Agents

3.14.19.1. Indications

Short term use for managing situational anxiety.

3.14.19.2. Dose and Related Information

• Benzodiazepines.

• Lorazepam (Ativan) (0.25 mg - 1 mg per dose) administer lowest effective dose; relatively short acting (up to 4 hours); not to exceed four times daily; taper and discontinue when situational crisis resolved.

• Clonazepam (Klonopin) (0.25 mg - 2 mg per day) longer acting (8 hours), sedating benzodiazepine, not to exceed 3 doses per day.

3.14.19.3. Major Contraindications

• Sedation, respiratory depression and risk for falls.

• Tolerance; these agents are not intended for long term use.

• Behavioral disinhibition; although anxiety is the target symptom, higher doses may produce intoxication and behavioral disinhibition characterized by increased impulsivity and a failure to respond to noxious consequences.

• Abrupt discontinuation can cause seizures.

3.14.19.4. Non-benzodiazepine Anxiolytics

• Hydroxyzine (Atarax, Vistaril) (25 mg - 50 mg per dose up to 4 times daily); an antihistamine that initially causes sedation, then habituation with anti-anxiety effect after a few days; can be used for itching of the skin.

• Gabapentin (Neurontin) (100 mg - 300 mg per dose, as needed or up to 3-4 times daily). Duration of effect is 4-6 hours. Higher doses may be used at hour of sleep for sleep induction.

3.14.19.5. Major Contraindications

• Special dose considerations for renal or hepatic dysfunction.

• Sedation, respiratory depression and risk for falls.

- Tolerance; not intended for long term use.
- Gastro-intestinal upset.

3.14.20. Antipsychotics

3.14.20.1. Indications

- Treatment of psychosis, agitation and impulsive aggression in PWS [2]. Risperidone is the only antipsychotic medication with international consensus for use in PWS but must monitor for weight gain.

3.14.20.2. Dose Related Information

- Due to increased sensitivity to drug dosage in PWS from an abnormal body composition, a lower drug dose (*e.g.*, about one-half usual dosage) may initially be administered and then a higher dosage prescribed depending on clinical response.
- Risperidone: Risperdal (0.25, 0.5, 1, 2, 3, 4 mg tablets) 0.25 mg/day orally; increase at intervals of no shorter than 1 week, titrated to address target symptoms; not to exceed 6 mg/day.
- Aripiprazole: Abilify (2, 5, 10, 15, 20 tablets) 1-2 mg/day (or every other day in young children); titrate slowly, but be aware of the possibility of mood and behavioral activation; not to exceed 20 mg /day.
- Ziprasidone: Geodon (20, 40, 60, 80 mg capsules) 20 mg twice daily with food, may increase based on clinical response to 80 mg twice daily.
- Olanzapine: Zyprexa (2.5, 5, 7.5, 10, 15, 20 mg tablet) 2.5 mg/day and increase by 2.5 mg/day weekly until target symptoms resolve or dose reaches 20 mg/day.
- Quetiapine: Seroquel (25, 50, 100, 200, 300, 400 mg tablet) 25 mg/day and increase by 25mg/day in multiple doses to 400 mg/day. Quetiapine SR (50, 150, 200, 300, 400 mg tablet) is the long acting form and can be started at 50 mg at hour of sleep. It is effective for treating bipolar depression at doses of 300-400 mg/day at hour of sleep.
- Haloperidol: Haldol (0.5, 1, 2, 5, 10, 20 mg tablets) 0.25 mg/day; titrate as tolerated. Not to exceed 10 mg/day.

3.14.20.3. Major Contraindications

- Atypical antipsychotics are noted to increase appetite and weight gain in typical persons, but this is less likely to occur in persons with PWS who have controlled food access, which is the standard of care for PWS. Pharmacogenetic testing results appear to play a role [89, 90].
- Risperidone is associated with elevated prolactin levels and gynecomastia. Adding a very low dose of aripiprazole can reverse this symptom.
- Aripiprazole can cause mood and behavioral activation even at low doses.
- Ziprasidone has been noted to increase QT interval on Electrocardiogram (ECG), so baseline ECG should be obtained and monitored during increases in dose.
- Olanzapine has been noted to contribute to the occurrence of metabolic syndrome, but it is a highly effective mood stabilizer with anxiolytic properties. It also causes sedation and is therefore best administered at the hour of sleep.

3.14.20.4. Comments

- Monitor weight, waist circumference, blood pressure and pulse at each appointment.
- Monitor fasting blood glucose and fasting lipids.
- Monitor for Extrapyramidal Symptoms (EPS) and tardive dyskinesia each visit. Muscle rigidity may not be appreciated in PWS due to hypotonia, but the loss of emotional expression in the face and loss of associated arm swing while walking are more reliable indicators of EPS. The occurrence of tremor is variable. EPS are best managed by reducing the dose of the antipsychotic medication, as treatment with anticholinergic agents will increase side effects. Although the risk of withdrawal dyskinesias and tardive dyskinesia is less with the use of second generation atypical antipsychotics, both of these disorders have been seen in persons with PWS and ongoing monitoring with an AIMs test at each medication visit is recommended.
- The risk of neuroleptic malignant syndrome (NMS) appears to be the same in PWS compared to typical persons. Assessment of neuroleptic malignant syndrome is complicated by hypotonia, unreliability of fever in PWS and pre-existing autonomic instability in PWS. NMS is a medical emergency that requires prompt treatment with lorazepam and possibly dopamine agonists.
- Long before atypical antipsychotics were available, haloperidol was used with some success to manage the behavioral outbursts in PWS. It is still used in individuals who do not respond to atypical antipsychotics.
- The class of atypical antipsychotics has been helpful for treating behavioral problems as well as mood instability. However, because some of the newer agents, such as aripiprazole activate serotonin receptors, they carry the same risk of producing a syndrome of mood and behavioral activation as do the SSRIs.

3.14.21. Mood Stabilizers

3.14.21.1. Indications

- Treatment of bipolar disorder, intermittent explosive disorder and picking behaviors in PWS.

3.14.21.2. Dose and Related Information

- Lithium: Begin at a dose of 300 mg/d orally and titrate to a dose of 300 mg three times daily, increasing at intervals of no shorter than 1 week. Obtain trough serum lithium levels until the desired mood and behavioral response is achieved, or until dose–related side effects of tremor or polyuria prohibit higher dosing. Levels of up to 1 mEq/L may be required for impulsive aggression and up to 1.5 mEq/L may be required for mania. If polyuria becomes a significant clinical symptom while mood and behavior are improved at steady state lithium levels, reduce the total daily dose by one-third and administer all of it at the hour of sleep; this reduces the renal side effects without compromising efficacy.
- Carbamazepine/oxcarbazepine (Tegretol/Trileptal): Begin at a dose of 100 mg orally twice daily; increase at inter-

vals of no less than 1 week. Obtain serum electrolytes at a dose of 300 mg bid to rule out hyponatremia (see below). Between doses of 600-900 mg/d in persons with PWS, there is a high likelihood that hyponatremia will prohibit the titration to optimal doses necessary to obtain mood and behavioral benefit. The addition of lithium carbonate at less than therapeutic levels is an effective way to decrease free water and increase serum sodium in PWS. The use of diuretics or oral supplementation with salt tablets is not effective.

• Valproic acid/sodium valproate (Depakote): Begin at a dose of 250 mg daily and increase to 250 mg twice daily after one week and then to three times daily, titrating the dose to a trough serum level of between 50-100 mcg/L. Higher doses are required for management of mania. Monitor liver function, platelet count and serum ammonia levels. Non-hepatic hyperammonemia is linearly related to total daily dose and duration of treatment; it increases throughout the developmental period in persons with PWS. It responds to dose reduction or discontinuation. Fine tremor is seen at higher doses.

• Topiramate (Topamax): Begin at a dose of 25 mg/d orally; increase at intervals of no less than 1 week, not to exceed 200 mg daily. Doses of 25 mg three times daily have shown some benefit with skin picking in PWS [101, 102]. Monitor serum electrolytes for increasing chloride and decreasing bicarbonate indicative of hyperchloremic acidosis (see contraindications below).

• Lamotrigine (Lamictal): Begin at a dose of 25 mg/d and titrate very slowly by 25 mg every 2 weeks due to the risk of Stevens Johnson rash. Attenuated dosing is required with concurrent use of valproic acid. Doses up to 400 mg/d in divided doses are tolerated without difficulty. Lamotrigine has been helpful for self-injury related to emotional dyscontrol (gouging or cutting) or depression associated with bipolar disorder.

3.14.21.3. Major Contraindications

• Carbamazepine/oxcarbazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds or concurrent use of monoamine oxidase inhibitors. There is a dose related incidence of hyponatremia when using oxcarbazepine in PWS (> 600 mg /day); serum sodium levels of less than 130 mEq/L have been associated with seizures. There is an additive risk of hyponatremia when these agents are used in combination with other psychotropic agents, such as SSRIs or atypical neuroleptics. CBC and differential must be obtained due to the risk of neutropenia and thrombocytopenia. There is also a risk of Stevens Johnson rash. Pharmacogenomic testing of HLA antigens can help to manage the risk of rash.

• Topiramate is a carbonic anhydrase inhibitor. It can cause renal tubular acidosis, resulting in a hyperchloremic metabolic acidosis that leaches calcium from bone, worsening risk of osteoporosis in PWS. It is for this reason that topiramate has been associated with hypercalciuria and the development of kidney stones. Also, it has been reported to cause cognitive blunting and irritability at higher doses.

• Valproic acid should not be used in patients with impaired liver function or impaired bleeding time. It should not be used in individuals with mitochondrial disorder, as this increases the risk of hyperammonemia.

3.14.21.4. Comments

• It may take weeks to months at therapeutic doses to appreciate the full efficacy of mood stabilizers.

• Lithium: Obtain baseline values of thyroid, serum electrolytes and renal function. Both TSH, T4 and T3 levels should be obtained at baseline because of the risk of mixed central and peripheral hypothyroidism. Obtain thyroid function (TSH, T4 and T3) at 6 weeks after maximum dose has been achieved and monitor every 6 months thereafter. Hypothyroidism occurs in up to one-third of patients receiving lithium. Monitor kidney function and lithium levels at regular intervals, as there is a narrow therapeutic index. A dose adjustment of lithium may be required when it is used in conjunction with gabapentin due to additive effects on renal dysfunction. There are reports of secondary hyperparathyroidism associated with long term lithium use. Serum calcium levels should be monitored and if hypercalcemia occurs, then parathyroid hormone levels should be obtained.

• Carbamazepine/oxcarbazepine: Monitor CBC and differential for agranulocytosis and thrombocytopenia. Monitor serum electrolytes for hyponatremia.

• Topiramate: Can increase the risk of kidney stones by 2-4 times. Use caution in patients with hepatic or renal impairment; a dose reduction may be necessary. Monitor serum electrolytes for decreasing bicarbonate and rising chloride, indicators of metabolic acidosis. Although topiramate has been used for weight reduction in individuals with binge eating disorder and to reduce cravings in individuals with addictions, there is no evidence that topiramate has any effect on the food related behaviors in PWS.

• Valproic acid: Monitor liver function, platelet count and serum ammonia (specimen must be placed on ice immediately, so levels should be obtained at a hospital laboratory).

• Systematic studies evaluating the benefits and safety of anticonvulsant mood stabilizers in adolescents or adults with PWS are not available.

3.15. Vitamins and Other Supplements

3.15.1. Calcium

3.15.1.1. Indications

Prevention of osteopenia/ osteoporosis in PWS.

Recommended daily intake:

• Ages 1-3: 700 mg/d orally.

• Ages 4-8: 1000 mg/d orally.

• Ages 9-18: 1300 mg/d orally.

• Ages 19-70: 1000 mg/d orally.

• Ages > 70: 1200 mg/d orally.

3.15.1.2. Comments

Daily recommended intakes are based upon values determined by the Institute of Medicine.

3.15.2. Vitamin D

3.15.2.1. Indications

Prevention of osteopenia/osteoporosis in PWS.

Recommended daily intake:

- Ages 1-70: 600 IU/d orally.
- Ages > 70: 800 IU/d orally.

3.15.2.2. Comments

- Vitamin D should be taken in conjunction with calcium supplementation.
- Daily recommended intakes are based upon values determined by the Institute of Medicine.

3.15.3. Omega-3 Fish Oils

3.15.3.1. Indications

Fatty acid supplementation; mood and behavior stability; prevention of seasonal affective disorder.

Recommended daily intake:

- 1000 mg three times daily with meals.

3.15.3.2. Comments

The calorie restriction in the diet of persons with PWS at any age may sacrifice fats, including healthy fat sources from meat and fish. Fatty acids are essential for maintenance of neuronal membranes, essential to neuronal function and may also reduce inflammation.

3.15.4. N-acetyl Cysteine (NAC)

3.15.4.1. Indications

NAC has been shown to be effective in treating the skin picking associated with PWS [93]. It is available as a capsule and a dissolvable fizzy (PharmNac).

Recommended starting dose: 600mg once daily. Increase to 600 mg twice daily after 6 weeks and increase by 600 mg every 6 weeks up to 1200mg twice daily.

3.15.4.2. Comments

NAC is a powerful peripheral antioxidant and modulator of the interaction between glutamate and GABA neurotransmitters in the brain. It has been used extensively for the treatment of acetaminophen overdoses in children and frequently used during radiographic procedures that require contrast media. Recently, it has been found to be effective in treating refractory trichotillomania at doses up to 2400 mg/d in typical adults. It has also been effective in managing ritualistic and repetitive behavior in autistic spectrum children at doses of 900 mg TID [93].

3.16. Non-drug Treatments

3.16.1. Section Content and Questions to Answer

Surgical and other procedural interventions including radiation therapy and other non-surgical modalities and ancillary medical care such as respiratory care, nutritional support, physical therapy and lifestyle measures will be discussed using bulleted format. Such modalities will be listed in an order that reflects acuity of care and the usual progression of applicability provided in subsections on: Description, indications, complications and comments. EBM entries will be provided at the end of each subsection, if indicated and summarized with effectiveness provided.

3.16.2. Assisted Feeding (infancy)

3.16.2.1. Description

- Techniques used to feed infants with inability to suck.
- Manual assistance with sucking may be tried with the use of special nipples, but in some cases, nasogastric or gastrostomy tubes may need to be placed in order to ensure adequate delivery of nutrients.

3.16.2.2. Indications

- Failure to thrive in infants with PWS.
- Tube feedings are usually reserved as a final resort after intensive efforts at nursing have failed.

3.16.2.3. Complications

- Potential deleterious metabolic or cardiovascular effects of excessive weight gain, if infants are over-fed with this method.

3.16.2.4. Comments

- There are no data addressing the optimal method for assisted feeding techniques in infants with PWS but observe closely for aspiration and aspiration-related pneumonia.

3.16.3. Weight Management

3.16.3.1. Description

- Dietary and physical activity counseling and strategies implemented to prevent obesity.

3.16.3.2. Indications

- All children with PWS should begin a weight management program at the onset of hyperphagia.

3.16.3.3. Comments

- When hyperphagia develops, caloric restriction at 60% of the recommendations for non-PWS children or about 8 to 11 kilocalories per centimeter of height per day to maintain weight and 7 kilocalories per centimeter of height per day to lose weight should be established. In adulthood, 800-1000 kilocalories per day is often needed to lose weight and 1200 kilocalories per day to maintain weight for non-GH treated individuals with PWS. GH therapy and exercise plans now commonly in use in PWS at all ages may require different calorie intake per individual [2, 26, 84, 85].
- Increased physical activity (*e.g*., 30 minutes per day of using an exercise bike) is recommended to assist in preventing and treating obesity. In some individuals with PWS, an increased caloric intake (*e.g*., 1800 kcal/day) can be utilized if exercise sessions last for extended periods of time (such as 45-60 minutes) [84].
- Other weight management strategies: locks on the refrigerator and pantry, limited amounts/types of food available in the home, non-food related rewards, reduced portion size at

mealtime using smaller dishes, encouraging participation in meal planning.

• Psychological food security manages the anxiety that results from uncertainty about food. It clarifies expectations around daily food access and limits the disappointment that inevitably leads to emotional upset and tantrums. Food security consists of knowing the meal plan (specific foods and portions served), knowing when the meals and snacks will be served across the day and assuring there will be no opportunity to acquire any other food.

• Bariatric surgery to decrease gastric size and thus lower caloric intake has been explored as an option to reduce appetite and treat obesity, but is not recommended due to complications of gastric necrosis, increased risk for gastric rupture and skin excoriation of the suture site in PWS.

3.16.4. Orthopedic Bracing or Surgery

3.16.4.1. Description

• Procedures may be required to correct spinal curvature in younger children or adolescents with scoliosis. Scoliosis is not affected by PWS genetic subtypes but those with higher weights or BMI may develop kyphotic deformities with scoliosis and are at a higher risk for surgical intervention. Associated limb malalignment is also more common in PWS when scoliosis occurs and often includes foot abnormalities.

3.16.4.2. Indications

• Bracing is recommended for curves of 20 to 40 degrees to prevent progression.

• Surgery is indicated for severe, early onset scoliosis in adolescents near skeletal maturity if bracing is not successful.

3.16.4.3. Complications

• There is an apparent increased risk for paraplegia associated with orthopedic surgery for scoliosis in PWS but with improved complication rates noted with newer spinal instrumentation. However, complications from surgery can occur at a higher rate in PWS with anesthesia use, a narrow airway, poorer lung capacity and mechanics due to decrease muscle mass and strength with hypotonia requiring longer recovery room time and self-injury (picking at the incision site) following the operation impacted by increased pain tolerance. Due to decreased bone density in PWS, orthopedic procedures may be more difficult technically and with delayed healing and recovery.

• Deep infections and pneumonia may occur in up to 30% of cases as self-injury (skin picking) at incision sites with increased pain tolerance are noted in PWS which delays healing leading to infections and complications.

3.16.4.4. Comments

• Orthopedic assessment is recommended prior to initiating rhGH therapy.

3.16.5. Orchiopexy

3.16.5.1. Description

• Surgical treatment of an undescended testicle by freeing and implanting it into the scrotum.

3.16.5.2. Indications

• Male infants with cryptorchidism (undescended testes).

3.16.5.3. Complications

• Mispositioning of the relocated testis or testes.

• Devascularization of the testis cord leading to testis atrophy.

• Division of the vas deferens.

3.16.5.4. Comments

• Orchiopexy should be performed within the first year of life because scrotal hypoplasia and/or obesity can make surgery difficult to perform. The likelihood of success for orchidopexy in males with PWS and hypogonadism is lower than in other males with un- descended testicles without PWS.

3.16.6. Tonsillectomy and Adenoidectomy

3.16.6.1. Description

• Surgical removal of tonsils and adenoids.

3.16.6.2. Indications

• Obstructive sleep apnea (OSA) in the presence of enlarged tonsils and adenoids and as the first line of treatment. CPAP is recommended if adenotonsillectomy is not performed or if OSA persists postoperatively and with pulmonary edema.

3.16.6.3. Complications

• Post-operative hemorrhage.

• Pain, potentially leading to dehydration.

• Airway obstruction due to local edema or hemorrhage.

3.16.6.4. Comments

• Tonsillectomy and adenoidectomy may be advisable to treat obstructive sleep apnea in children prior to commencing rhGH therapy. Weight loss is recommended in addition to other therapy in children who are overweight or obese.

• Individuals with PWS are prone to having a small or narrow airway which requires special attention when intubating.

3.16.7. Ophthalmologic Surgery

3.16.7.1. Description

• Surgical procedure to correct strabismus, performed with purpose of either restoring single binocular vision or eliminating anomalous head position.

3.16.7.2. Indications

• Performed on patients with intermittent esotropia if deviation is poorly controlled. Signs of poor control include presence of manifest deviation more than 50% of individual observations, failure to recover normal alignment after a blink during testing, decrease in stereo acuity and overall impression of surgeon that control is worse.

3.16.7.3. Complications

• Ocular perforation with suture needle as tendon is reattached to globe.

• Diplopia in patients who cannot suppress image from one eye and whose visual axes are misaligned after surgery.

3.16.7.4. Comments

• Bilateral surgery may be necessary to correct strabismus.

3.16.8. Behavioral Therapy

3.16.8.1. Description

• Form of intervention that focuses on modifying patterns of behavioral interaction to manage maladaptive conduct.

3.16.8.2. Indications

• Children with PWS who display behavioral problems including excessive repetitive behavior, impulsivity, aggression, property theft or destruction, self-injury, angry outbursts, temper tantrums and oppositional defiance.

3.16.8.3. Comments

• Behavior management works best by rewarding desired behaviors and providing low attention, when possible, to undesirable behaviors, particularly in early childhood. Consultation with an Applied Behavioral Analyst may help to identify antecedents to maladaptive behaviors, patterns of caregiver response that sustain maladaptive behaviors and interventions to enable incremental change.

• Behavior management should include incentives besides rewards and also consequences which are explained to the individual.

• Skin picking can be lessened by reducing boredom or providing diversion with sensory rich alternatives to behavior (popping bubble pack, playing with yarn, etc.).

• For behavioral issues such as impulsivity, aggression, food theft, property destruction and self-injury, therapeutic approaches should include a provision of a controlled environment with a daily schedule, exercise programs and supervision.

• Reinforcement, food security, regular monitoring, provision of a safe environment, anger management and social skills training should all ideally be included in the therapy plan.

• Data are limited for addressing optimal behavioral treatment plans for all ages of persons with PWS and specific behavioral problems.

3.16.9. Speech Therapy

3.16.9.1. Description

• A set of counseling techniques used to improve speech and verbal skills.

3.16.9.2. Indications

• Pragmatic language delay and articulation abnormalities in infancy and childhood.

3.16.9.3. Comments

• There are no data on effectiveness but yet used commonly in clinical practice.

3.16.10. Special Circumstances

3.16.10.1. Comorbidities

• Ordered by importance. Identify special populations, comorbid conditions, medications or treatments that influence management strategies. Explain how management would be adjusted for these populations (*e.g*. how pregnancy alters the approach to treating tuberculosis). Use bulleted format. How do other patient characteristics or concomitant diseases affect management?

• Endocrine disturbances may include hypothyroidism and central adrenal insufficiency which is seen in about 10% of PWS individuals [86].

• Increased risk of seizures (less than 5%) and temperature instability in PWS particularly during infancy, childhood and adulthood. Adults with PWS have been reported with body temperatures below 90º F but without a known cause. Idiopathic hyper- or hypo-thermia may occur during minor illnesses, anesthesia and psychotropic use. PWS individuals may not respond normally to infection, *i.e*., fever may not be present despite extensive infection [2].

• Gastroparesis, gastric necrosis and gastric rupture, a high pain threshold and lack of vomiting may occur. PWS individuals may not respond normally to abdominal distention or pain from life-threatening gastric inflammation or necrosis. These life-threatening complications should be monitored under close supervision and to avoid hyperphagia leading to these problems [57].

• Osteoporosis, scoliosis and fractures are common in PWS along with hip subluxation. Monitoring for scoliosis with radiological skeletal surveys by 18 months of age is recommended and if present then bracing and/or surgical intervention may be required over time. Growth hormone treatment commonly prescribed in PWS infants, children and adolescents and growth rate should be followed closely using PWS specific growth charts (70). Growth hormone can improve bone density and therefore lessen osteoporosis risk, increase muscle mass and strength which would improve surgical outcomes, if surgery is undertaken [2]. Surgical complications can occur at a higher rate in PWS with anesthesia use, a narrow airway, poorer lung capacity and mechanics due to decrease muscle mass and strength with hypotonia requiring longer recovery room time and self-injury (picking at the incision site) following the operation with increased pain tolerance. Also, decreased bone density can further cause problems with orthopedic surgical procedures and healing. In addition, the Growth Hormone Receptor (GHR) is involved in the initial step of growth hormone action and influenced by GHR gene polymorphisms contributing to the response of growth hormone, the ligand for GHR and affect the rate of growth [67, 103]. An increased growth rate due to increased sensitivity to growth hormone *via* GHR in the presence of decreased muscle mass and marked hypotonia in PWS theoretically increases the frequency and severity of scoliosis in affected individuals. More research is needed to determine the role of GHR gene polymorphisms as biomarkers for scoliosis in PWS. Analysis of circulating mediators of bone remodeling in PWS has demonstrated involvement of Receptor Activator of Nuclear Factor-Kappa beta Ligand (RANKL), Osteoprotegrin (OPG) and sclerostin

in bone turnover in PWS [104]. These molecules may play a role in decreased bone density seen in this syndrome (66) and may be targets to treat and improve bone health in PWS.

• Neurotransmitter levels may be disturbed in PWS due to a decrease in GABA receptor subunits from three GABA receptor subunit genes in the 15q11-q13 region deleted in the majority of PWS patients. This could alter the response to anesthesia or sedative agents such as propofol and delay recovery time following surgery. This deficit in GABA tone also predisposes to tantrums, psychoses and catatonia. Other medical concerns in PWS include unusual reactions to standard dosages of medication and anesthesia during infancy or later due to metabolic differences from a decreased muscle mass and increased obesity. A narrow airway may be present and certain agents (*e.g*, GABA receptor agonist agents for sedation) could lead to uncommon anesthesia and medication reactions with prolonged recovery time following surgery [56].

• Enamel hypoplasia, dental caries, dry mucosal membranes and decreased salivary secretion are common in PWS. Poor oral hygiene, bruxism and rumination can also negatively impact on the soft tooth enamel. Special toothbrushes can improve hygiene and products to increase salivary flow are encouraged. Dental examinations should begin at or before two years of age [2].

• Because hypopigmentation is due to a deletion of the P gene seen in most PWS patients, they are at risk of developing melanoma and skin carcinoma. Protection against ultraviolent exposure with sunscreen and clothing to inhibit sun exposure are recommended to lessen the malignancy risks. The decreased pigment may also affect retinal pigment and visual acuity. Hence, an ophthalmology evaluation is indicated in infancy or early childhood to address vision problems and to monitor for myopia and strabismus [2].

• Learning disabilities are very common among children with PWS. Although psychoeducational testing is performed by school districts, neuropsychological testing may provide a more informed blueprint upon which IEP recommendations can be made. Every child should have a 504 plan for PWS related to hyperphagia.

• Symptoms of autistic spectrum phenotype are higher among individuals with the maternal disomy 15 genetic subtype. This has been attributed to increased gene expression such as the UBE3A gene, a ubiquitin ligase that has epigenetic effects and associated with autism in non-PWS individuals [105]. A small number of children with maternal disomy 15 are nonverbal, display high rates of stereotypic behaviors and meet the criteria for Autistic Spectrum Disorder (ASD); however, they do not display the characteristic hyperphagia associated with PWS and actually, seek social proximity. A study from Japan examined ADHD symptoms and ASD traits from preschool age throughout the developmental period among a cohort of children with the paternal 15q11-q13 deletion vs maternal disomy 15. They identified no differences between the groups in early school age, but those with maternal disomy 15 displayed increased symptoms of ADHD in middle school followed by social withdrawal and decreased social skills in adolescence. Children with the 15q11-q13 deletion continued to acquire social skills throughout the developmental period [106].

• Stress sensitivity in PWS predisposes to mood disorders. In addition to decreased GABA tone, there are abnormalities in the function of the serotonin system in PWS. Faulty editing of the serotonin 2C receptor is due to the deletion of a small nucleolar (sno)RNA HBII-52 (SNORD115) located in the PWS critical region [107]. Loss of the imprinted snoRNA mbii-52 leads to increased 5htr2c pre-RNA editing and altered 5HT2CR-mediated behaviour. Comorbid anxiety, depression and bipolar disorder increase with age. The incidence of bipolar disorder and cyclic psychosis reaches 85% by age 30 among those with the maternal disomy 15 [108]. There is increased risk for psychosis in either genetic subtype. Furthermore, recent studies examining clinical neuropsychiatric aspects in a cohort of adults with PWS residing at group homes found significantly more neuropsychiatric findings in those with the larger 15q11-q13 Type I deletion compared with those with the smaller 15q11-q13 Type II deletion after adjusting for age [109].

• The top reported causes of death in PWS are respiratory failure (31%), cardiac (16%), gastrointestinal (10%), infection (9%), obesity (7%), pulmonary embolism (7%), choking (6%) and accidents (6%) and survival trends described [40, 110, 111].

4. CONCLUSION

4.1. Patient Satisfaction/Lifestyle Priorities

4.1.1. Section Content and Questions to Answer

Disease and treatment that affects lives and activities of people with PWS including different lifestyles will be discussed using bulleted format describing the impact on disease and treatment for patients and their families.

The quality of life in PWS is directly related to hyperphagia and adverse outcomes associated with obesity. Many persons with PWS will ask for restrictive management of food. Also, the level of adaptive function is rarely commensurate with measured intellectual ability and more consistent with the emotional quotient [112].

4.2. Consultation

4.2.1. Section Content and Questions to Answer

Consultation for treatment decisions and therapeutic procedures will be discussed in a bulleted format and outlined with advice needed from experienced consultants in treating the patient with PWS. Situations requiring specialists input for management and what specialties to be consulted will be addressed.

A multidisciplinary team of consultants is required for the care of infants, children, adolescents and adults with PWS with the care coordinator being a specialist, depending on the age and individual needs of the patient, in the field of pediatrics, clinical genetics, endocrinology or neurology with support from learning/behavioral experts and dietitians. A neonatologist may be involved for medical care and intervention due to the feeding difficulties, hypotonia and diag-

nostic issues while genetic counseling will be important for family members and for delivery of syndrome-specific information. Other consultants may include developmental pediatrics, speech and language specialists, orthopedics, physical therapy, dentist, sleep disorder specialists, ENT specialists, ophthalmology, gastroenterology, pulmonary, urology, gynecology, cardiology, psychiatry and psychology may eventually become involved. A key member of the team will be a registered dietitian for input on caloric intake with macro- and micro-nutrient surveys is required throughout the life of a person with PWS.

4.3. Monitoring

4.3.1. Section Content and Questions to Answer

In bulleted format, outlined appropriate plans for monitoring disease and treatment with specific metrics and timelines will be discussed including recommendations for PWS:

- Monitoring of body weight or body mass index should be an ongoing process throughout the lifespan of an individual with PWS as increased weight can contribute to other health issues (fatty liver, high lipid, cholesterol and glucose levels), orthopedic problems (stress or deformed joints, scoliosis, kyphosis), skin lesions with infection and cardiovascular/pulmonary problems. From infancy through 18 years of age, the weight should be maintained between the 25th through 75th percentile according to established syndrome-specific PWS growth charts [68, 69]. Growth charts for those PWS subjects treated with growth hormone from infancy to 18 years of age have also been reported [70]. In adults, the goal is to prevent overweight and obesity. Weight management strategies are discussed under "Non drug treatments."

- A pediatric endocrinologist should be involved to assess for the presence and monitor the evolution of endocrine disorders, including thyroid, adrenal and growth hormone deficiencies. Occur at diagnosis and periodically thereafter (*e.g.*, every 6 months during infancy and yearly at later ages). Growth hormone therapy may be continued into adulthood in some individuals.

- Basal morning cortisol levels should be measured to monitor for central adrenal insufficiency and stimulation testing performed specifically before initiation of growth hormone treatment or planned surgery. Stress doses of glucocorticoids should be administered empirically during episodes of critical illness or prior to surgery unless adrenal insufficiency has been ruled out by recent prior provocative testing.

- Insulin resistance and Type 2 diabetes mellitus, often develop secondary to obesity in PWS, do occur but respond to weight loss as seen in the general population. Medications to mitigate insulin resistance may also be considered in consultation with an endocrinologist on an individual patient basis. Fasting glucose and lipid levels are often monitored at ~6-month intervals.

- Hypogonadism is present in both males and females with puberty being arrested or incomplete. Testosterone (in males) and estrogen (in females) treatment should be considered depending on the age of the patient at the time of pubertal onset and during adult-hood. Males are thought to be infertile but a few PWS females have established pregnancies. About one-third of appropriately aged PWS females develop menstruation but with irregular cycles. Serum inhibin B is the best indicator of fertility.

- Osteoporosis and osteopenia should be monitored with bone density measurements by DXA. Consultation with an orthopedic expert specializing in bone metabolism is recommended. The use of calcium and vitamin D supplements and weight bearing exercises is often advised. Scoliosis may worsen during growth hormone treatment and growth acceleration should be monitored closely with skeletal x-ray series and bone age studies (*e.g.*, yearly).

- Enamel hypoplasia, dental caries and dry mucosal membranes with decreased salivary secretion are common in PWS which can lead to choking on food. Poor oral hygiene, bruxism and rumination can also negatively impact on the soft tooth enamel. Special toothbrushes can improve hygiene and products to increase salivary flow are also encouraged. Annual or biannual dental examinations should begin at or before two years of age.

- Recent studies suggest that individuals with PWS of all ages may suffer from dysphagia due to abnormal esophageal motility. Increasing fluids during and after a meal while pacing the food bolus may lessen the risk of choking, improve mastication and facilitate an efficient swallow.

- Individuals with PWS carry an elevated risk for melanoma and other skin cancers, in association with skin hypopigmentation. Protection against ultraviolent exposure with sunscreen and clothing to inhibit sun exposure are recommended to lessen the malignancy risks. The decreased pigment may also affect retinal pigment and visual acuity. Hence, an ophthalmology evaluation is indicated at an early age to address vision problems and to monitor annually for myopia and strabismus in infancy or early childhood.

4.4. Prognosis

4.4.1. Section Content and Questions to Answer

In a bulleted format, the usual course of disease is outlined, both short- and long-term with treatment or without is discussed. Information will include morbidity and mortality, potential for relapse and recurrence and possible disease outcomes.

4.4.1.1. Introduction and Background

Prognosis depends on transition from stage 1 (failure to thrive) to stage 2 (hyperphagia and obesity) of clinical course development; monitoring obesity status and managing with food and dietary control, psychological food security and mandatory exercise for calorie expenditure; determining mental capacity and identifying and treating neurological/psychiatric findings (*e.g.*, seizures, autism, aberrant behavior, mental illness and psychosis); monitoring the endocrine, orthopedic, cardiopulmonary and gastrointestinal systems to avoid health related complications (*e.g.*, diabetes, scoliosis, hypertension and heart failure, apnea, gastric necrosis) and death [2].

- Many complications are common in PWS and will adversely impact morbidity and mortality, such as obesity,

heart failure, apnea and diabetes. If left untreated or unresolved, these complications will shorten the life expectancy.

- Death typically occurs in the fourth decade of life with average age of females of 31 years and 29 years in males; but if weight control is successful, then PWS adults may live into their seventh decade or beyond. Unfortunately, choking-related deaths do occur at an early age [2, 40, 109].

4.5. Complications

4.5.1. Section Content and Questions to Answer

A list and discussion of the most common complications of both disease and treatment for PWS and how complications can affect further management and outcomes will be discussed including common complications of the disease listed with treatments related to PWS.

4.5.2. Complications Seen in Prader-Willi Syndrome

PWS is associated with findings related to obesity (if weight is not adequately controlled). The associated complications and co-morbidities of obesity include:

- Diabetes mellitus.
- Hypertension.
- Orthopedic problems.
- Osteoporosis.
- Obesity hypoventilation and right-sided heart failure.
- Fatty liver.
- Hypoventilation with hypercarbia and CO2 narcosis.
- Obstructive sleep apnea and narrow airway.
- Stasis ulcers and cellulites.
- Variable degree of mental deficiency and illness (delayed cognitive development, learning problems, psychiatric co-morbidity).
- Behavioral problems such as outbursts, self-injury, tantrums, food stealing, repetitive asking and hoarding.
- Endocrine disturbances such as obesity, diabetes, short stature and growth hormone deficiency, adrenal insufficiency, hypothyroidism, sex hormone and reproductive problems.
- Neurological disorders such as seizures, temperature instability, hypotonia, autonomic nervous system dysfunction, hyperphagia.
- Musculoskeletal disorders, such as scoliosis, hip subluxation, kyphosis, osteoporosis, fractures, decreased muscle mass.
- Disturbed energy balance and metabolism (decreased physical activity and strength, lower metabolic rate).
- Gastrointestinal problems (constipation, delayed gastric emptying, gastroparesis, gastric inflammation, gastric necrosis and rupture, decreased salivary secretions and swallowing difficulty including choking on food and silent aspiration, rumination, bruxism, increased ghrelin production, leading to enhanced reward from eating).
- Water intoxication from excessive drinking, altered vasopressin secretion and/or use of diuretic medication can lead to abnormal electrolyte levels.
- Respiratory issues, including a narrow airway passage, low muscle tone and strength and sleep apnea, collectively lead to an increased chance of aspiration pneumonia.
- Hyperthermia and hypothermia.

4.6. Secondary Prevention/ Patient Education

4.6.1. Section Content and Questions to Answer

Measures to prevent recurrent disease or its complications in treated patients with PWS will be listed in a bulleted format and measures advised to prevent relapse or recurrence will be presented, if applicable. Elements of essential information for patients about diagnosis, treatment and follow-up will be provided including web resources appropriate for patient use to know about the disease, treatment, prognosis and other implications.

4.6.1.1. Introduction and Background

Family caretakers for patients with PWS should be informed of the following:

- Infants with PWS should be handled carefully due to their poor muscle tone.
- Hypotonia is an ongoing risk factor for sensory motor deprivation in infancy that may result in sensory hunger (sensory seeking form of sensory motor processing difficulty) later in development, so ongoing intensive infant stimulation services are required.
- Decreased arousal and decreased tone in the facial muscles of emotional expression in early infancy can interfere with emotional bonding between infant and parent, so coaching for persistent infant stimulation is necessary.
- Individuals with PWS must be monitored carefully for weight gain and due to hyperphagia, access to food in the house must be restricted at a later age in early childhood. To avoid complications from obesity, monitoring caloric intake will be a lifelong activity in PWS.
- In addition to controlled food access, individuals with PWS benefit from psychological food security, best described by the paradigm no doubt, no hope, no disappointment. This means that the person knows with certainty and accepts the conditions surrounding their diet plan, including menu, portion control and meal schedule. This assures that the behavioral manifestations of disappointment will not occur.
- Exercise is an essential part of the daily plan for a person with PWS. It provides energy expenditure, sensory motor stimulation, deep breathing increased alertness and stress relief.
- Children with PWS must be monitored with testing for numerous complications of PWS and caretakers must keep up with scheduled testing and outcome results measured.
- Individuals with Prader-Willi syndrome require specialized care and supervision throughout adulthood and most live in residential care facilities for safety, to avoid compli-

cations of obesity and to provide supervised access to appropriate work, leisure skills and socialization with peers.

The following websites are recommended to educate families caring for a child with PWS.

• www.pwsausa.org - Prader-Willi Syndrome Association (USA) is an organization of families and professionals working together to raise awareness, offer support, provide education and advocacy and promote and fund research to enhance the quality of life of those affected by Prader-Willi syndrome.

• Utah Medical Home Portal - www.medicalhomeportal.org - Review and information about providing care on Prader-Willi syndrome by primary care physicians, other health care providers and parents to address health care needs.

4.7. Practice Performance Measures/Summary of Evidence

4.7.1. Section Content and Questions to Answer

Standard performance indicators and a brief statement of the rule by which each is applied, as defined by Centers for Medicare and Medicaid Services (CMS), Joint Commission and others as appropriate will be provided and discussed on measured standards for quality of care. A summary of the EBM entries will be given.

4.7.1.1. Introduction and Background

• A meta-analysis studying the effect of rhGH therapy on body composition in adults with PWS identified 8 studies that included 134 individuals treated with rhGH for 12 months. Treatment of individuals with PWS with rhGH led to (weighted mean difference (MD) 95% confidence interval (CI)) reduced body fat (MD: -2.9%; CI: -3.90 to -1.910), visceral fat (MD: -32.97 cm^2; CI: -55.67 to -10.26), subcutaneous adiposity (MD: -55.24 cm2; CI: -89.05 to -21.22), and increased lean body mass (MD: 2.41 kg; CI: 1.32 to 3.49). Studies of longer duration confirmed the findings for change in body fat (MD: -2.89%, CI: -4.69 to -1.07) and lean body mass (MD: 2.82 kg; CI: 1.31 to 4.33). Individuals treated with rhGH for 12 months did exhibit small increases in fasting glucose (MD: 0.27 mmol/L; 95% CI: 0.05 to 0.49) [87].

• A multicenter prospective trial studied the effects of long-term continuous rhGH treatment on body composition, growth, bone maturation and safety parameters in children with PWS. Fifty-five prepubertal children (mean age of 5.9 ± 3.2 years) were followed over 4 years while treated with rhGH (1.0 mg/m2). Body fat percentage (SDS) was significantly lower after 4 years of rhGH treatment ($P < 0.0001$). Lean body mass SDS significantly increased during the first year of treatment ($P = 0.02$) but returned to baseline values the second year and remained unchanged thereafter. Mean ± SD height normalized from -2.27 ± 1.2 SDS to -0.24 ± 1.2 SDS ($P < 0.0001$) after treatment with rhGH. Body mass index SDS significantly decreased. Thus, body composition and height were significantly improved in children with PWS after long-term treatment with rhGH. No adverse effects were noted on bone maturation, blood pressure, glucose homeostasis and serum lipids [91].

• A Randomized Controlled Trial (RCT) studied the effects of rhGH treatment on cognitive functioning in 50 prepubertal children (ages 3.5 to 14 yr) with PWS. Cognitive functioning was measured biennially by validated intelligence tests (the Wechsler Preschool and Primary Scale of Intelligence-Revised, Dutch version (WPPSI-R) or the Wechsler Intelligence Scale for Children-Revised, Dutch version (WISC-R)). Total Intelligence Quotient (IQ) score was estimated based on two subtest scores. After 4 years of GH treatment, mean standard deviation scores (SDS) on the Similarities and Block design subtests were significantly higher than at baseline (Mean Difference (MD); 95% Confidence Interval (CI)) for Similarities test- MD: +0.4; 95% CI: -0.1 to 0.7; $P = 0.01$ for Block Design- MD: +0.3; CI: 0.07 to 0.6, $P = 0.01$. These results indicate that long-term GH treatment significantly improves abstract verbal reasoning and visuospatial skills and reduces the gap between children with PWS and healthy controls on these skills. Thus, during long-term GH treatment, children with PWS developed their vocabulary at the same pace as healthy references. The mean estimated total IQ score improved 4 points during 4 years of GH treatment, but this result did not reach significance ($P = 0.2$) [92].

• Several clinical trials for treating hyperphagia and/or obesity in PWS have met with limited success [95] but other trials are proposed or planned for the future.

4.8. Guidelines

4.8.1. Section Content and Questions to Answer

Relevant current guideline(s) identified from established organizations/groups will be provided and concordant with screening, prevention, diagnosis and treatment sections. There are at least five established peer-reviewed and textbook sources of information on the treatment of individuals with Prader-Willi syndrome with cited references for recommenda-tions on diagnosis and management and portal home disease specific websites (*e.g*., medicalhomeportal.org). The reader is referred to the following published works for more in- depth assessment of care, diagnosis and treatment of Prader-Willi syndrome:

The Endocrine Society has published the following regarding Prader-Willi syndrome:

• Goldstone AP, Holland AJ, Hauffa BP, Hokken- Koelega AC, Tauber M. Recommendations for the diagnosis and management of Prader-Willi syndrome. J Clin Endocrinol Metab 2008; 93: 4183-97.

The American Academy of Pediatrics has published the following regarding Prader-Willi syndrome:

• McCandless SE. Clinical report-health supervision for children with Prader-Willi syndrome. Pediatrics 2011; 127: 195-204.

The International Prader Willi Syndrome Organization has published the following regarding Prader-Willi syndrome:

• Best Practice Guidelines for Standard of Care in PWS (2010) JL Forster (Ed), N Hoedebeck-Stuntebeck and H Soyer (Publishers) www.ipwso.org

Additional resources and websites related to care, diagnosis and treatment in Prader-Willi Syndrome:

• Cataletto M, Angulo M, Hertz G, Whitman B. Prader-Willi syndrome: A primer for clinicians. Int J Pediatr Endocrinol 2011; 18, 12.

• Online Mendelian Inheritance in Man (OMIM) [http://www.omim.org/].

• Hoybye C (eds.): Prader-Willi Syndrome. Nova Science Publisher, Inc., Hauppauge, New York 2013: p.1-294.

• Butler MG, Welch J, Riske M, Vogel R, Troxell R, Rope A. Prader-Willi Syndrome Website Module, www.medicalhomeportal.org:9090/diagnoses-and- conditions/prader-willi-syndrome/.

• Butler MG, Roberts J, Hayes J, Tan X, Manzardo AM. Growth hormone receptor (GHR) gene polymorphism and Prader-Willi syndrome. Am J Med Genet A 2013; 161A(7): 1647-1653.

• Buiting K, Cassidy SB, Driscoll DJ, *et al*. Clinical utility gene card for: Prader-Willi syndrome. Eur J Hum Genet 2014; 22(9). doi: 10.1038/ejhg.2014.66.

• Prader-Willi Syndrome Association [PWSA (USA)] [http://pwsausa.org/].

• Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012: 130, e714-55.

• Vogels A, De Hert M, Descheemaeker MJ, *et al*. Psychotic disorders in Prader-Willi syndrome. Am J Med Genet A 2004; 127A: 238-243.

4.9. Diagnostic Codes (ICD9-759.81 and ICD10-Q87.1) for Prader-Willi Syndrome

4.9.1. Clinical and Parent Questions

4.9.1.1. Section Content and Questions to Answer

Five of the most important clinical questions (with answers that can be found in the text) will be provided by a clinician treating a patient with PWS and five questions that patients are most likely to ask will be presented.

4.9.2. Clinical Questions

What causes Prader-Willi syndrome?

• PWS is a genomic imprinting disorder caused by loss of expression of genes from the chromosome 15q11- q13 region that are expressed only on the father's chromosome 15 usually due to a deletion of the chromosome region from the father.

What are the most common features seen in patients with Prader-Willi syndrome?

• The cardinal features are infantile hypotonia, a poor suck with feeding problems and failure to thrive, growth hormone deficiency with short stature and small hands and feet, hypogonadism/hypogenitalism, hyperphagia and onset of obesity in early childhood if not controlled and learning/behavioral problems.

What tests should be ordered to confirm the clinical suspicion of PWS?

• DNA methylation testing of the chromosome 15q11- q13 region is undertaken to identify the abnormal PWS methylation pattern using methylation-based PCR or MS-MLPA using several probes in this region. Historically, FISH analysis with probes in the 15q11-q13 region was used to identify deletions in the region. MS-MLPA is also used to not only identify the 15q11-q13 methylation status but also to identify deletions. Now, chromosomal microarrays with SNP probes are used to identify the presence or absence of the 15q11-q13 deletions but also to determine whether maternal disomy 15 is present and the subclass (maternal heterodisomy 15, segmental isodisomy 15 or total isodisomy 15. If the 15q11-q13 deletion, segmental isodisomy 15 or total isodisomy 15 are not identified using SNP microarrays, then genotyping with DNA markers from chromosome 15 is performed on the PWS patient and parents. An imprinting defect of chromosome 15 is present if biparental (normal) inheritance of chromosome 15 is found in the PWS child after examining the DNA pattern from the mother, father and child.

What is the suggested treatment once the diagnosis is confirmed?

• Although there is no cure, growth hormone therapy is indicated to treat the growth hormone deficiency and to improve stature, decrease fat mass and increase muscle and strength. Diet intervention with reduced caloric intake and exercise programs to avoid obesity are recommended throughout the lifespan of an individual with PWS.

What is the prognosis for a patient with PWS?

• Prognosis depends on early diagnosis and treatment with growth hormone and other therapies including stimulation programs to maximize learning, potential and diet intervention to control caloric intake and to lessen obesity and its complications thereby improving the quality of life and lifespan.

4.9.3. Parent Questions

What causes Prader-Willi syndrome?

• PWS is a genomic imprinting disorder caused by loss of expression of genes from the chromosome 15q11- q13 region that are expressed only on the father's chromosome 15 usually due to a deletion of the chromosome region from the father.

Was there something that I did that caused Prader-Willi syndrome to occur in my child?

• PWS is due to errors in genomic imprinting usually due to a deletion of the chromosome 15q11-q13 region which is not from anything that the mother or father did or did not do to cause the condition. PWS is due to a genetic event that occurred at or around the time of conception.

Is there a cure or treatment for Prader-Willi syndrome?

• There is no cure but treatment with growth and other hormones, diet and exercise plans to lessen the likelihood of obesity and gaining access to therapies (physical, occupation, speech) are warranted. Educational and behavioral

treatment plans are helpful to improve the quality of life and to increase life expectancy. Consultation with a clinical geneticist and genetic counselor would be encouraged to answer questions and to provide information useful to the family (and patient) would be encouraged.

What are the chances that it will occur in future children?

• The recurrence risk is generally less than 1% but in rare cases (*e.g*., imprinting center defect) the risk may be as high as 50%. Therefore, genetic evaluation and counseling are indicated to determine and discuss the chance for recurrence depending on the genetic subtype which should be determined as it may impact not only on the recurrence risk but also for treatment and prognosis.

What can I expect from my child with Prader-Willi syndrome (will my child die early, attend school, live independently, have children)?

• For newly diagnosed infants and children with PWS, the prognosis is improved with better care and treatment with growth and other hormones. Avoidance of obesity and its complications to improve life expectancy is a lifelong goal and if successful the live expectancy approaches normal. Hyperphagia remains a constant problem which lowers the likelihood for independent living. Children with PWS do attend school in regular classroom settings but may require individual educational programs to maximize their learning ability and progress but close supervision (and access) to food sources is required. PWS males are thought to be sterile although there have been a few PWS females who have established and maintained pregnancies giving birth to live born unaffected children. Those PWS females with the 15q11-q13 deletion are at risk (*i.e*., 50%) of having offspring with Angelman syndrome.

CONSENT FOR PUBLICATION

Written informed consent has been obtained from both patients for using their images in the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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