# Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome

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**Context:** Recombinant human GH (rhGH) therapy in Prader-Willi syndrome (PWS) has been used by the medical community and advocated by parental support groups since its approval in the United States in 2000 and in Europe in 2001. Its use in PWS represents a unique therapeutic challenge that includes treating individuals with cognitive disability, varied therapeutic goals that are not focused exclusively on increased height, and concerns about potential life-threatening adverse events.

**Objective:** The aim of the study was to formulate recommendations for the use of rhGH in children and adult patients with PWS.

**Evidence:** We performed a systematic review of the clinical evidence in the pediatric population, including randomized controlled trials, comparative observational studies, and long-term studies (>3.5 y). Adult studies included randomized controlled trials of rhGH treatment for ≥ 6 months and uncontrolled trials. Safety data were obtained from case reports, clinical trials, and pharmaceutical registries.

**Methodology:** Forty-three international experts and stakeholders followed clinical practice guideline development recommendations outlined by the AGREE Collaboration (www.agreetrust.org). Evidence was synthesized and graded using a comprehensive multicriteria methodology (EVIDEM) (http://bit.ly.PWGHIN).

**Conclusions:** Following a multidisciplinary evaluation, preferably by experts, rhGH treatment should be considered for patients with genetically confirmed PWS in conjunction with dietary, environmental, and lifestyle interventions. Cognitive impairment should not be a barrier to treatment, and informed consent/assent should include benefit/risk information. Exclusion criteria should include severe obesity, uncontrolled diabetes mellitus, untreated severe obstructive sleep apnea, active cancer, or psychosis. Clinical outcome priorities should vary depending upon age and the presence of physical, mental, and social disability, and treatment should be continued for as long as demonstrated benefits outweigh the risks. (***J Clin Endocrinol Metab* 98: E1072–E1087, 2013)**

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Abbreviations: BMI, body mass index; ENT, ear, nose, throat; GHD, GH deficiency; HbA1c, glycated hemoglobin; PWS, Prader-Willi syndrome; RCT, randomized controlled trial; rhGH, recombinant human GH; SDS, SD score.

Prader-Willi syndrome (PWS) is a rare genetic disorder (OMIM #176270) characterized by hypotonia, poor feeding in infancy, hyperphagia with evolving obesity, hypogonadism, decreased adult height, and cognitive and behavioral disabilities (1, 2).

The birth incidence of PWS is difficult to ascertain, but data from several studies suggest that it is at least 1 in 25 000 live births. PWS is genetically heterogeneous; in approximately 65–70% of patients, PWS results from a deletion of the paternally inherited chromosomal 15q11.2–q13 region (DEL15); in 25–30%, from maternal uniparental disomy for chromosome 15 (UPD15); whereas approximately 1% of patients have imprinting defects (ID) or translocations involving chromosome 15 (2, 3).

The therapeutic rationale for the use of recombinant human GH (rhGH) is derived from our understanding of the comorbidities seen in PWS, which resemble those seen in association with GH deficiency (GHD) (eg, reduced muscle strength, altered body composition, low energy expenditure, and reduced growth, even in the presence of obesity). Although the etiology of impaired GH secretion in PWS remains controversial due to the common occurrence of obesity, the serum levels of IGF-I are reduced in most children (4–6) and adults (7) with PWS, and excess body fat is seen in even nonobese affected children (8, 9). Reduced GH responses to a variety of GH secretagogues, as well as decreased 24-hour spontaneous GH release, have been documented in 58–100% of affected children (10). Information regarding GH secretory pattern in adult patients with PWS is more limited and suggests more variability, with many potential explanations (7, 11–13).

Short-term rhGH treatment of children with PWS was first reported in 1987 (14). It has been used by many members of the international medical community and advocated by parental support groups since its approval by the Food and Drug Administration in 2000 for use in children with PWS, based on short-term growth data and subsequently for its effects on body composition. However, the use of rhGH therapy for this condition represents a unique therapeutic challenge that includes treating individuals with cognitive disability, varied therapeutic goals that are not focused exclusively on increased height (15), and concerns about potential life-threatening adverse events (16).

Prior expert consensus documents discuss the general care of patients with PWS, including some discussion of rhGH therapy in children and adults with PWS (17, 18), although many questions remained, particularly about the effects on functional outcome and on long-term body composition changes. Recent pertinent publications have since appeared (19–29), and the Growth Hormone Research Society therefore held a Consensus Workshop to systematically review the literature and grade the available evidence (30, 31) and provide concise recommendations for the use of rhGH in this context with adherence to the Principle of Respect for Persons (32) as the guiding ethical principle for rhGH use in PWS (ie, provision of care and protection of patients who do not have autonomy).

The objective of the workshop was to evaluate the effects of rhGH therapy in pediatric and adult patients with PWS and provide evidence-based guidelines for its use, summarized herein.

## Workshop Methodology

Forty-three experts (pediatric and adult endocrinologists, clinical and basic geneticists, epidemiologists, a nutrition specialist, an orthopedic surgeon, a psychiatrist, health technology assessment specialists, a bioethicist, a health economist, and a patient advocate; see author list in *Acknowledgments*) participated by invitation from the scientific committee (see author list). Clinical representatives from 5 manufacturers of rhGH also submitted their PWS-specific safety data.

Prior to the workshop, an extensive literature review based on a multicriteria methodology (30, 31) was performed to identify relevant available data concerning rhGH treatment for patients with PWS. For clinical evidence in the pediatric population, randomized controlled trials (RCTs) (20–26, 33–41), comparative observational studies (42–48), and long-term studies (>3.5 y) (5, 49–58) were included. Adult studies included RCTs of rhGH treatment for ≥ 6 months (7, 29, 59, 60) and uncontrolled trials (61–64), because data were more limited. Safety data from pharmaceutical registries (phase 4 trials)[1] and sponsored clinical trials (phase 3) were reviewed. Data on disease, therapeutic context, and economic, ethical, and societal aspects were also included to reflect a broad international context. Details on approach, evidence tables, and data summaries are available in Supplemental Table 1, sections A and B (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) and on the workshop web site (http://bit.ly/PWGHIN; Ref. 65).

The level of evidence was evaluated using the scoring procedure based on the Oxford Centre for Evidence-Based Medicine (CEBM) Level of Evidence scale (66). Strength

[1] National Cooperative Growth Study (Genentech), Genetics and Neuroendocrinology of Growth International Study (Lilly), Kabi International Growth Study (Pfizer), GH Moniter (EMD Serono), Nordinet and ANSWER (Novo Nordisk).

of evidence (Supplemental Table 1, section C) was graded independently by 2 of the authors (C.L.D. and M.T.) using the EVIDEM Quality Assessment instrument (30, 67), and a quality grade on a 4-point scale (low to excellent) was then assigned to each publication. In the rare cases of disagreement, the study was re-examined jointly.

Synthesized information by criteria was then provided to workshop participants before the workshop discussions as follows: 1) for validation of content; and 2) to provide background information to answer relevant questions concerning GH and PWS (Supplemental Table 2).

Based on 2 days of structured talks and breakout sessions, participants formulated and categorized levels of recommendations using the following system:

A. Evidence or general agreement that a given procedure of treatment is beneficial, useful, and effective.
B. Weight of evidence is in favor of usefulness or efficacy.
C. Usefulness or efficacy is less well established by evidence or opinion.
D. Evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful.

To each recommendation, a CEBM level of evidence score was assigned to reflect the origins of the data that led to the recommendation.

## Overview of Evidence Quality

Multiple pediatric RCTs with rhGH have reported statistically significant effects in patients with PWS on growth, body composition, resting energy expenditure, motor development (infants and children), muscle strength, exercise tolerance, bone health, and lipid profiles (20–26, 33–41, 50). Overall, these trials have been performed in small populations, and durations were short compared to the length of rhGH treatment in the real-life setting; quality grade ranged from low (10 publications) to high (1 publication). There is only 1 placebo-controlled study (35) and 1 controlled dose-response study (34) in the pediatric population, although the adult trials include placebo-controlled groups (7, 29, 59, 60). Most patients had genetically confirmed diagnoses. Methodological issues were noted in several studies, including incomplete reporting of patient numbers, lack of discussion of randomization methods, rare inclusion of intent-to-treat analyses, limited statistical details (*P* values only), and minimal information about important confounders (eg, socioeconomic status, degree of adherence to diet, exercise plan). Only 2 studies reported individual patient responses (26, 33).

It is difficult to criticize the validity of these studies based on flawed methodologies because the effects are consistent at least in the short term (1-y data), as demonstrated by recent meta-analyses in children and adults (19, 28). There are data regarding clear benefits to rhGH treatment in infants, childhood, adolescence, transition to adulthood, and in young adulthood, but there are less long-term data available after the fourth decade.

## Summary of Recommendations

The workshop participants established 15 recommendations dealing with rhGH use in PWS, as shown in Table 1.

Considerations specific to each recommendation are briefly summarized here.

## Baseline Evaluation of the GH-IGF Axis Before rhGH Treatment

Previous expert opinions (17) have suggested that GH testing is not necessary in children with PWS, although some countries require it in order for treatment reimbursement. It was agreed that over 50% of infants and children with PWS are, or will become, GH deficient by standard testing protocols (4, 10, 26, 38, 50, 68–72). No consensus was reached concerning the frequency of testing in cases where GH sufficiency is initially documented. Determining the presence of GHD after attainment of adult height may be beneficial, however, because reports from dynamic testing in adults suggest that GHD is not universal, and many countries require testing before treatment of adults with GHD (28). It is not known whether GH secretory status predicts metabolic response to rhGH treatment. Furthermore, within a research context, and in order to increase our understanding of genotype-phenotype relationships, GH testing may be desirable. Because serum IGF-I is a useful biomarker for monitoring compliance with treatment as well as sensitivity to GH, all participants agreed that baseline IGF-I levels should be determined.

## Additional Considerations Prior to Starting rhGH Treatment

All participants agreed that evaluation of patients before beginning treatment should ideally include a complete assessment coordinated by a multidisciplinary team with expertise in PWS, as summarized in Table 2. This stems from the importance of diagnosing and treating comorbidities that may impact on GH safety as well as on GH response.

**Table 1.** Summary of Clinical Care Guidelines for rhGH Therapy in PWS

| | |
|---|---|
| I. | After genetic confirmation of the diagnosis of PWS, rhGH treatment should be considered and, if initiated, should be continued for as long as demonstrated benefits outweigh the risks. (Recommendation level A; level of evidence 1) |
| II. | GH stimulation testing should not be required as part of the therapeutic decision-making process in infants and children with PWS. (Recommendation level A; level of evidence 3) |
| III. | Adults with PWS should have an evaluation of the GH/IGF axis before rhGH treatment. (Recommendation level A; level of evidence 4) |
| IV. | Before initiation of rhGH therapy, patients with PWS should have a genetically confirmed diagnosis and expert multidisciplinary evaluation. (Recommendation level A; level of evidence 5) |
| V. | Exclusion criteria for starting rhGH in patients with PWS include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis. (Recommendation level A; level of evidence 4) |
| VI. | Scoliosis should not be considered a contraindication to rhGH treatment in patients with PWS. (Recommendation level A; level of evidence 2) |
| VII. | Infants and children with PWS should start with a daily dose of 0.5 $mg/m^2 \cdot d$ sc with subsequent adjustments toward 1.0 $mg/m^2 \cdot d$ every 3–6 mo according to clinical response [*] and guided by maintenance of physiological levels of IGF-I [**]. (Recommendation level A; level of evidence 1[*] or 5[**]) |
| VIII. | Adults with PWS should receive a starting dose of 0.1–0.2 mg/d based on age, presence of edema, prior rhGH exposure and sensitivity, and concomitant oral estrogen use. Subsequent dosage titration should be based on clinical response, age-, and sex-appropriate IGF-I levels in the 0 to +2 SDS range. (Recommendation level A; level of evidence 2) |
| IX. | Selection of patients with PWS for rhGH therapy and dosing strategy should not depend on the genetic class of PWS (DEL15; UPD15; ID). (Recommendation level A; level of evidence 2) |
| X. | IGF-I levels in patients with PWS on rhGH treatment should be maintained within the upper part of normal range (maximum + 2 SDS) for healthy, age-matched normal individuals. (Recommendation level B; level of evidence, 3 [adults] or 5 [children]) |
| XI. | Clinical outcome priorities should vary depending on age and on the presence of physical, mental, and social disability. (Recommendation level A; level of evidence 1) |
| XII. | Monitoring of rhGH treatment in patients with PWS should address specific benefits and risks of treatment in this population and the potential impact of other hormonal deficiencies. (Recommendation level A; level of evidence 3) |
| XIII. | Patients with PWS receiving rhGH must be followed carefully for potential adverse effects during GH treatment. (Recommendation level A; level of evidence 1) |
| XIV. | Treatment with rhGH must be in the context of appropriate dietary, environmental, and lifestyle interventions necessary for care of all patients with PWS. (Recommendation level A; level of evidence 4) |
| XV. | Cognitive impairment should not be a barrier to treatment with rhGH for patients with PWS. (Recommendation level A; level of evidence 4) |

Recommendation levels: A, evidence or general agreement that a given procedure of treatment is beneficial, useful, and effective; B, weight of evidence is in favor of usefulness or efficacy; C, usefulness or efficacy is less well established by evidence or opinion; and D, evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful. Levels of evidence: 1, systematic review of randomized trials; 2, randomized trial or observational study with dramatic effect; 3, non-RCT/follow-up study; 4, case-series, case-control, or historically controlled studies; and 5, mechanism-based reasoning.

Product labeling information for all of the rhGH preparations commercially available (regardless of approved diagnosis) lists several contraindications to rhGH use, including acute critical illness, severe obesity or severe respiratory impairment, active malignancy, active proliferative or severe nonproliferative diabetic retinopathy, and hypersensitivity to the product. Workshop participants acknowledged these exclusion criteria and felt that active psychosis should also be included. Psychiatric illness is now increasingly recognized in patients with PWS (73).

Careful attention should be given to the clinical criteria used to define severe pediatric obesity because there are no clear definitions as in adults (body mass index [BMI] > 40 $kg/m^2$). Workshop participants felt it prudent to consider obesity in the pediatric population with PWS as "severe" if a child with a BMI over the 95th percentile manifests complications of obesity such as sleep apnea, nonalcoholic fatty liver disease, or abnormalities of carbohydrate metabolism. Because treatment with rhGH decreases insulin sensitivity, uncontrolled diabetes mellitus, regardless of the presence or absence of diabetic complications such as retinopathy, demands attention before initiation of rhGH therapy in patients with PWS.

Children with PWS have a high incidence of both central apnea and obstructive apnea (74–77). Marked obesity or intercurrent respiratory tract infection (often underdiagnosed because of the absence of fever), can exacerbate obstructive apnea and may even lead to sudden death (78–82). Because rhGH therapy can theoretically lead to lymphoid tissue growth in children due to increased IGF-I effects (83), patients and parents must be fully informed about the potential association between rhGH therapy and unexpected death during the pretreatment consenting process, and polysomnography should be performed before starting therapy. rhGH therapy is contraindicated in children with breathing difficulties until ear, nose, throat (ENT) evaluation and treatment of respiratory-compromising obesity has been achieved. Therapy should not be initiated dur-

**Table 2.** Multidisciplinary Evaluation of Pediatric and Adult Patients with PWS Before Starting rhGH Treatment[a]

| Evaluation | Testing/Interventions |
|---|---|
| Endocrine examination to document anthropomorphic status: weight, length/height, BMI (and if possible, waist circumference and skinfold thickness), pubertal status, and presence of additional endocrine deficiencies | Bone age determination in infants and children<br>Evaluation of hypothyroidism (TSH, free $T_4$, free $T_3$) and commencement of replacement if appropriate<br>Determination of IGF-I level and, if possible, GH response to provocative testing, particularly in adult individuals<br>Evaluation of metabolic status if age ≥ 12 y and obesity: HbA1c, fasting insulin and glucose; consider oral glucose tolerance test if family history of diabetes, acanthosis nigricans or ethnic risk factors<br>Evaluation of cardiovascular risk profile as per guidelines for obese individuals:[b] fasting total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol<br>Assess for hepatic steatosis as per guidelines for obese individuals:[b] AST and ALT levels, abdominal ultrasound, and biopsy where appropriate<br>Body composition evaluation if available (dual-energy x-ray photon absorptiometry or bioelectrical impedance)<br>Consider need for evaluation of adrenal function on an individual basis |
| Genetic evaluation and counseling | DNA studies to confirm PWS |
| Referral to dietician | Nutritional evaluation and advice including use of food diary, control of food environment, diet composition, and caloric intake |
| Assessment of developmental and cognitive status | Age-appropriate psychomotor testing |
| Assessment of motor function if possible | Physiotherapy and occupational therapy referral |
| ENT referral if history of sleep-disordered breathing, snoring, or enlarged tonsils and adenoids are present | Tonsillectomy and adenoidectomy where indicated |
| Referral to pneumologist/sleep clinic | Sleep oximetry is mandatory before starting rhGH in all patients, preferably completed by polysomnographic evaluation |
| Scoliosis evaluation and referral to orthopedic surgeon if indicated | Spine x-ray |
| Family instruction on rhGH treatment including benefits and risks of the treatment and importance of careful monitoring | Procurement of legal guardian consent and patient assent/consent according to age and cognitive status |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Adapted and modified from A. P. Goldstone et al: Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2008;93(11):4188 (17), with permission. © The Endocrine Society.

[b] For guideline references in obesity, see Refs. 127–129.

ing an acute respiratory infection, but it need not be interrupted during subsequent episodes of respiratory infection unless indicated because of the onset of breathing difficulties.

Scoliosis in PWS is not a contraindication to rhGH treatment; its occurrence is common (up to 30–80% depending on age), but neither its incidence nor its rate of progression is influenced by rhGH therapy (21).

The potential role of the GH-IGF axis in cancer incidence and/or progression has received a great deal of recent attention (84) despite the safety record, to date, of rhGH treatment. The recent SAGhE study publications do not specifically address rhGH use in patients with PWS, and a true appreciation of dose-related risks of rhGH will require better and longer surveillance protocols because all observational studies are subject to bias (85–88).

The potential development of central adrenal failure, which may not be clinically relevant except during intercurrent illness and/or surgical intervention, was also discussed. Investigations have not uniformly documented a high incidence of central adrenal failure in PWS (89–91). No consensus was reached concerning the need for adrenal axis testing before initiation of rhGH, but families and clinicians should remain vigilant and not hesitate to use stress doses of glucocorticoids as clinically indicated.

## Age at Treatment Initiation

According to observational data, rhGH treatment is usually initiated at a mean age of 7 years, as reported by Takeda et al (92). Increasingly, rhGH treatment is initiated earlier (10, 17, 71). Published data support benefits of rhGH treatment when started between 4 and 6 months of age (25, 34), but some experts are currently treating from as early as 3 months. No consensus was reached on age of rhGH start, although all agreed to the benefits of treating before the onset of obesity, which often begins by 2 years of age.

## Dosing

### Infants and children

Evidence for efficacy in infants and children is based on trials using a dosage of 1.0 $mg/m^2 \cdot d$ achieved within approximately 1 month of starting treatment (50). Given that patients with PWS exhibit variable degrees of GHD and that salutary outcomes in RCTs were associated with doses of 1.0 $mg/m^2 \cdot d$ (higher than the dose of rhGH routinely used in congenital GHD) or higher, it is unknown whether similar outcomes could be replicated with rhGH doses that result in consistently normal IGF-I levels. IGF-I levels and IGF-I/IGFBP-3 ratios rise to above 2 SD in some patients on this dosage, theoretically presenting some risk (26, 35, 38, 40, 51, 84, 93, 94). The efficacy of doses lower than 1.0 $mg/m^2 \cdot d$ administered over a long period of time is unknown; however, it has been suggested that the efficacy of lower doses of rhGH on body composition is decreased (50, 51). Infants and children with PWS should start with a daily dose of 0.5 $mg/m^2 \cdot d$ sc to minimize side effects, with subsequent adjustments toward 1.0 $mg/m^2 \cdot d$; there was disagreement as to how rapidly this should occur (3–6 mo). If not using body surface area-based calculations (recommended), it was felt prudent to base dose calculations on a nonobese weight for height in cases where overweight for height (BMI = 85th to 95th percentile) or obesity exists, particularly when starting rhGH therapy. There was a difference of opinion regarding the timing and frequency of IGF-I measurement before increasing dosage to 1.0 $mg/m^2 \cdot d$ in the pediatric population with PWS. Notably, patients with PWS appear to be highly sensitive to GH in terms of IGF-I generation (95), and standard rhGH dose often results in IGF-I levels outside the normal range. Because lymphoid hyperplasia is related to the levels of IGF-I (96), this might increase the risk of sleep apnea (81).

### Adults

In adults with PWS, rhGH doses tested in placebo-controlled and open-label trials have varied between 0.2 and 1.6 mg/d sc, depending on the time period under rhGH treatment, weight, and induced IGF-I levels. This dose range gives an acceptable side effect profile (29, 59, 61–64, 97), as well as beneficial effects on body composition, psychological and behavioral problems, quality of life, and heart function and results in IGF-I levels within the range of age-matched controls (59, 61, 63, 64, 97, 98). It was unanimously concluded that in adults with PWS, the optimal IGF-I level, ie, the level where the rhGH treatment will have clear beneficial effects and at the same time the lowest possible risk of adverse events, will be a value similar to 0 to +2 SD score (SDS, z-score) for age-matched controls.

## Monitoring and Potential Side Effects

There was unanimous agreement that rhGH therapy should be supervised by pediatric or adult endocrinologists, ideally those experienced with the care of patients with PWS. Periodic monitoring of the safety and efficacy of the treatment is mandatory (Table 3).

In the past, rhGH therapy dose adjustments in children were routinely performed based on growth response and/or weight (or body surface area) increases. Epidemiological data suggesting a potential link between IGF-I levels and some adverse events (77, 84, 86, 99) have motivated investigators to consider maintaining IGF-I levels within the physiologically normal range (0 to + 2 SDS), an approach shown to be feasible in other conditions, such as rhGH treatment of children with idiopathic short stature or small for gestational age, where pharmacological doses are used (100, 101). Workshop participants felt that for the pediatric age range, IGF-I levels in patients with PWS on rhGH treatment could therefore safely be maintained within the upper part of normal range (+1 to +2 SDS) for healthy, age-matched normal individuals. For the adult population, where discontinuation of treatment because of side effects is more frequently noted, an IGF-I of 0 to +2 SDS was suggested.

Table 4 summarizes the side effects that should be routinely monitored. Although rhGH therapy has a favorable safety profile, the postulated association between unexpected death and rhGH treatment in children with PWS deserves special attention not only in the consenting process and pretreatment evaluation, but also during treatment (16, 83, 98, 102). During rhGH treatment, changes in breathing (particularly during sleep) should be promptly reported and evaluated by repeat oximetry and/or polysomnography within the first 3 to 6 months of starting therapy. Longer-term rhGH therapy has been associated with improvement in respiratory function in chil-

**Table 3.** Multidisciplinary Evaluation of Pediatric Patients[a] with PWS During rhGH Treatment[b]

| |
|---|
| Regular clinical assessment of height, weight, BMI, pubertal status, scoliosis, IGF-I, and side effects every 3–6 mo |
| Clinical assessment of body composition every 6–12 mo by 1 or more of the following: waist circumference, skinfold thickness, dual-energy x-ray absorptiometry (or other available technique for determining body fat and lean body mass) |
| Yearly bone age determination, particularly during pubertal age range |
| IGF-I determination every 6–12 mo |
| ENT assessment and sleeping oximetry, or ideally, repeat polysomnography within the first 3–6 mo |
| If development or worsening of sleep-disordered breathing, snoring, or enlargement of tonsils and adenoids, ENT assessment, polysomnography, and IGF-I measurement are mandatory. |
| Fasting glucose, insulin, and HbA1c; if obese and/or older than 12 y and/or acanthosis nigricans and/or family history of diabetes/ethnic risk factors, oral glucose tolerance test |
| X-ray ± orthopedic assessment if concern or doubt about scoliosis progression |
| Monitoring for hypothyroidism yearly or if symptoms occur |
| Lipid profiles and liver function tests and/or liver ultrasound according to family history, age, and weight status as per clinical guidelines for non-PWS patients, with referral to gastroenterologist if nonalcoholic fatty liver disease is suspected |
| In cases of acute illness and suggestive symptomatology, obtain critical blood samples for measurement of cortisol and ACTH levels, if possible, and assess adrenal glucocorticoid response to provocative testing where indicated |
| Continued contact with nutritionist, physiotherapist/occupational therapist, speech therapist, and psychologist (determine frequency on a case-by-case basis) |
| If marked deterioration in behavior with or without overt psychiatric symptoms, psychiatry assessment |

[a] Applicable to adult patients with PWS, with the exception of the radiological evaluations (bone age monitoring, scoliosis monitoring).

[b] Adapted and modified from A. P. Goldstone et al: Recommendations for the diagnosis and management of Prader-Willi syndrome. *J Clin Endocrinol Metab*. 2008;93(11):4188 (17), with permission. © The Endocrine Society.

dren and adults, primarily due to improvements in respiratory muscle function as indicated by increases in peak expiratory flow (35, 50, 97). Data concerning rhGH effects on central respiratory drive are few and are difficult to interpret because of multiple confounders (74, 103). No data are available concerning rhGH treatment and sleep apnea in adults with PWS.

There was a consensus to include an evaluation of diabetes risk (determination of glycated hemoglobin [HbA1c], fasting glucose, and insulin) in patients with PWS who are obese and/or who are older than 12 years or who have a positive family history of diabetes. Further studies are needed to refine these recommendations because insulin sensitivity and risk of metabolic syndrome in patients with PWS may vary depending upon degree of obesity, adipose tissue distribution, genetic background risk, and use of antipsychotics (104–108).

## Tolerability

Tolerability of rhGH by pediatric and adult patients with PWS is high, according to the workshop participants involved in RCTs (7, 24, 25, 29, 35, 36, 38, 41, 59–64, 97). However, relatively few adults with PWS have been studied, and insufficient data are available to judge whether adverse effects of rhGH, death due to other causes, or personal choice accounted for treatment cessation. For

**Table 4.** rhGH Potential Side Effects to Monitor[a]

| |
|---|
| Changes in physical features and body proportions (face, hands, feet) or bone growth |
| Peripheral edema |
| Joint pain |
| Sleep apnea/disordered breathing: snoring, respiratory pauses, excessive daytime sleepiness |
| Pseudotumor cerebri/benign intracranial hypertension: headache, visual changes, nausea, dizziness |
| Slipped capital femoral epiphysis: hip and/or knee pain, gait disturbance |
| Insulin resistance: elevated fasting insulin |
| Decreased $T_4$ level (requires measurement of $T_3$ to differentiate from true central hypothyroidism) |
| Scoliosis (recent data suggest no causal relationship or exacerbation of progression) |
| Long-term surveillance on, or after, cessation of rhGH |
| Glucose intolerance/type 2 diabetes mellitus particularly in obese patients or patients with positive family history |
| Epilepsy (no known relationship, but should be reported) |
| De novo neoplasia (no known relationship, but should be reported) |
| Stroke, intracranial bleeding |

[a] Shown are the reported side effects of GH treatment primarily in the pediatric population with or without PWS. No published data are available concerning GH treatment in adults with PWS on joint pain, sleep apnea, epilepsy, intracranial hypertension, neoplasia, and stroke/intracranial bleeding. Furthermore, none of the studies in PWS adults (longest follow-up, 5 y) have reported breast tenderness/enlargement, unexpected death.

children with PWS treated with rhGH and followed in phase 4 postmarketing surveys, the reported rate of side effects leading to treatment cessation in trials overall is low (109). The enthusiasm of parents of PWS children for rhGH therapy suggests that early cessation is lower than in other rhGH-treated patients with conditions like idiopathic short stature, Turner syndrome, and children who are born small for gestational age.

## Clinical Outcome Variables and rhGH Nonresponsiveness

In untreated children with PWS, auxological and body composition parameters tend to deteriorate over time, so if these continue to improve or to stabilize, treatment is usually continued until adult height or near-adult height is reached. However, if adult height attainment is used for the decision to stop rhGH therapy in adolescents with PWS, it is important to note that these patients often experience premature adrenarche and obesity, causing early closure of growth plates (110, 111).

For adults with PWS and GHD, treatment duration depends on primary clinical outcome (body composition, lipid metabolism, physical and psychosocial functioning) and occurrence of side effects (impairments of glucose metabolism, edema, heart disease) (62).

Controlled studies of continuous treatment through childhood, adolescence, and the transitional period into adulthood are not available in PWS, yet there is a strong likelihood of continued benefit by inference from non-PWS organic GHD and observational studies in PWS.

It was agreed that psychomotor development should be the priority during infancy, with body composition and growth becoming important during childhood and adolescence. The data on cognitive benefits of rhGH treatment in the pediatric setting are limited, but should positive effects be extended, this would likely become a top treatment priority (25, 26, 35, 112). The workshop participants concluded that metabolic outcome variables should become the important priority in adults with PWS, although muscular hypotonia, mental retardation, and psychosocial dysfunction should continue to receive attention throughout the life span. The ultimate goal is an improvement in the patient's well-being.

The definition of nonresponsiveness to rhGH is arbitrary because there is a continuum in GH response. Many other anthropomorphic and biochemical parameters plateau after some years of treatment but deteriorate subsequently if rhGH is stopped. Response criteria to rhGH will vary according to age, pubertal status, degree of growth retardation, and duration of therapy. Workshop participants felt that a successful first-year pediatric response to rhGH treatment includes a $\Delta$ height SDS $> 0.3$, a first-year height velocity increment of $\geq 3$ cm/y, or a height velocity SDS $\geq +1$. Workshop participants acknowledged the difficulty of having alternative, easily measurable, robust, validated, affordable clinical endpoints other than the initial growth response. When possible, attempts should be made to document favorable changes in psychomotor progress and development, body composition, strength and exercise tolerance, and quality of life for both patients and caregivers, and findings should be reviewed with all involved in the decision to continue treatment. Parameters that define the sustained success of therapy include adult height SDS, adult height SDS minus height SDS at start of rhGH, adult height minus predicted height at start of treatment, and adult height minus target height (based on sex-corrected mean parental height). Emerging data on genotype-phenotype correlations relevant to specific outcome measures targeted with rhGH therapy need to be repeated in additional cohorts before firm conclusions can be drawn (12, 102, 106).

## Use of Adjunct Therapies

Nutritional management remains the mainstay of treatment of patients with PWS, even during rhGH therapy. Regular contact with a dietitian knowledgeable about PWS is essential, initially to calculate desirable caloric increases during the failure-to-thrive period often observed in infants with PWS. Once the failure-to-thrive period is over, caloric requirements vary according to the nutritional phase of the patient and are typically approximately 80% those of children and adults without PWS (113). This entails surveillance of vitamin and trace element intake to ensure that recommended daily allowances are achieved. When hyperphagia begins, or if weight percentiles are increasing (usually ages 2–4 y), close supervision must be maintained to minimize food stealing. Locking the kitchen, refrigerator, and/or cupboards is often necessary. As members of the treating team, dieticians must regularly reinforce adherence to diet, environmental control, and programmed physical activity (114–116).

In some children, particularly those who have inadequate dietary, environmental, and/or lifestyle interventions, unacceptable weight gain may occur during therapy. All attempts should be made to sensitize the family as to the increased risks for obesity-related health concerns and to explain that rhGH therapy should not be viewed as a weight loss solution.

Recent studies in adolescent and adult patients with PWS (90% untreated with rhGH) using cyclic, intensive exercise and nutritional restriction successfully led to BMI reductions during the period of participation in the study (up to 6 y) (117). Long-term, rigorous exercise and strict nutritional control have not been tested against rhGH therapy at any age.

Multiple pharmacological approaches in PWS aimed at increasing energy expenditure and weight loss have not been successful in limited short-term trials and are summarized in Table 5. The workshop participants agreed that surgical strategies to achieve weight loss have not been

**Table 5.** Adjunct Therapies Attempted in PWS

| Pharmacological Strategies | Mechanism of Action | Limitations/Adverse Events | Refs. |
|---|---|---|---|
| Sibutramine | Noradrenergic reuptake inhibitor<br>Induces satiety without reducing metabolic rate | Modest weight loss efficacy<br>Poor long-term compliance<br>Hypertension | Padwal et al, 2007 (130) |
| Orlistat | Inhibits pancreatic lipase | Modest weight loss efficacy<br>Poor long-term compliance<br>Gastrointestinal side effects | Butler et al, 2006 (114) |
| Bupropion and naltrexone | Bupropion: activates central melanocortin pathways in the arcuate nucleus (α-MSH and β-endorphin secretion); decreases hunger and increases energy expenditure | Ineffective individually, some suggestion that combination therapy may be more effective at weight loss, no published clinical trials in PWS | Greenway et al, 2009 (131) |
| | Naltrexone: opioid inhibitor; blocks β-endorphin inhibition of α-MSH release (normal feedback disrupted); decreases hunger and increases energy expenditure | Multiple side effects: nausea, dry mouth, headache, dizziness, fatigue, constipation, insomnia, possibility of alteration of mood and depression | Lee and Fujioka, 2009 (132) |
| | | Contraindicated in acute hepatitis or liver failure | Padwal, 2009 (133)<br>Plodkowski et al, 2009 (134)<br>Zipf and Berntson, 1987 (135) |
| Antiepileptics (topiramate) | Antiseizure drug also used in migraine treatment | No published clinical trials in PWS | Shapira et al, 2002 (136) |
| | Modulatory effects on Na+ channels, GABAA, and AMPA/kainate receptors<br>Affects food-seeking behavior | Multiple side effects: fatigue, difficulty concentrating, paresthesia, somnolence, ataxia, dizziness, nephrolithiasis, word-finding difficulty, mild confusion, sedation | Smathers et al, 2003 (137) |
| Somatostatin analogs | Inhibits ghrelin secretion<br>Limits the release of insulin<br>Decreases hyperphagia | No benefits on weight or appetite in PWS<br>Decreased insulin secretion<br>Impaired glucose tolerance<br>Risk of cholesterol gallstones | De Waele et al, 2008 (138)<br>Haqq et al, 2003 (139)<br>Haqq et al, 2003 (140)<br>Tan et al, 2004 (141)<br>Tzotzas et al, 2008 (142) |
| Rimonobant | Blocks endocannabinoid receptor CB1 in central and peripheral nervous systems and other key cells involved in body energy metabolism | Efficacious weight loss<br>Lack of compliance in adults with PWS due to high risk of psychiatric side effects (mood disorders, suicide) | Motaghedi et al, 2010 (143) |
| Anorexigens gut hormones (eg, exenatide) | Incretin mimetic: GLP-1 receptor agonist<br>Increases insulin secretion | Lack of efficacy in subjects with PWS | Purtell et al, 2011 (144)<br>Sze et al, 2011 (145) |
| CoQ10 | Involved in the production of ATP in the mitochondria | No observed weight loss effects in PWS<br>Possible benefits on psychomotor development, but masked by the natural development | Eiholzer et al, 2008 (45) |

(Continued)

**Table 5.** Continued

| Pharmacological Strategies | Mechanism of Action | Limitations/Adverse Events | Refs. |
|---|---|---|---|
| Restrictive bariatric surgery (gastric banding or bypass) | Several surgical procedures | Contradictory efficacy results | Buchwald, 2005 (120) |
| | Induces weight loss by altering the digestive tract so that nutrients and fats are not absorbed by the body (stomach reduction and/or bypass) | Limited weight reduction long term | Antal and Levin, 1996 (119) |
| | | Numerous postoperative issues | Marinari et al, 2001 (122) |
| | | Weight regain 1 to 5 y after surgery | Papavramidis et al, 2006 (123) |
| | | Frequent complications from the resulting intestinal malabsorption (ie, nutritional deficiencies) | Marceau et al, 2010 (121) |
| | | Postoperative respiratory and infectious complications | Scheimann et al, 2008 (118) |
| | | Gastric perforation | |
| | | Death | |

Abbreviations: AMPA, $\alpha$-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; GABAA, $\gamma$-aminobutyric acid$_A$; GLP-1, glucagon-like peptide-1.

successful long term (initial weight loss followed by weight regain) and have been associated with frequent complications (intestinal malabsorption, infectious complications, gastric perforation, and death), and should therefore be discouraged (118–123).

Additional studies are required to ascertain the safety, efficacy, and tolerability of alternative pharmacological approaches to weight loss in PWS either alone or in combination with rhGH. Thus, there is insufficient evidence to support the use of currently available obesity management medications or bariatric surgery in conjunction with rhGH treatment for weight reduction in patients with PWS, and indeed, some may be contraindicated.

## Issues of Consent/Assent

There are differences in national legal regulations dictating when a child reaches the age of consent (eg, 18 y in many countries). Informed assent of a child is required in circumstances where he or she is beginning to make more complex decisions; this requires that the child is capable of some degree of understanding and appreciation of the clinical reasoning.

Even in cases of cognitive disability in an older child or adolescent with PWS, it is optimal that legal guardians remain surrogate decision-makers, but that physicians strive to obtain the patient's assent for rhGH therapy, even if the patient has limited decision-making capacity. An adult patient with intellectual disability due to PWS may be capable of consenting to rhGH treatment if he/she is able to understand and appreciate his or her clinical circumstances. In circumstances in which an adult patient does not have the capacity to consent, a surrogate decision-maker is appropriate, guided by country- and state-specific guardianship laws (124). This assent/consent process fosters a doctor–patient relationship based on partnership, mutual trust, understanding, and respect (32, 125, 126).

It is not known to what degree the cognitive impairment of the individual with PWS plays a role in physicians' lack of recommendation for rhGH use, whether because of perceived difficulty in obtaining truly informed consent or because of physicians' views on healthcare priorities. All participants felt that cognitive impairment should not be a barrier or a contraindication to discussion of rhGH treatment with the patient and caregivers.

## Issues of Fair Access to rhGH

According to several PWS support associations, access to the option of rhGH therapy is currently unevenly provided, even in countries with drug approval for this indication. Members of the workshop felt that several factors currently contribute to differences in the availability of the option for rhGH therapy for patients with PWS: 1) a lack of parental awareness of treatment options and general impediments to healthcare; 2) inadequate numbers of physicians willing and qualified to prescribe rhGH and to regularly assess treatment response and potential adverse events; and 3) inability to pay for rhGH either through personal wealth or by participation in a healthcare system that supports rhGH treatment and monitoring costs for PWS.

In considering efficiency and best distribution of healthcare resources among desirable interventions for patients with PWS, a long list of important interventions must be considered, such as occupational and physical therapy, speech and language therapy, social skills ther-

**Table 6.** Areas Regarding rhGH Use for PWS Requiring Prioritized Attention in Future Studies[a]

Top 10 areas for further research

i. Effects of rhGH therapy in adults with PWS on quality of life
ii. Long-term post-treatment effect of rhGH on mortality and morbidity using registries
iii. The optimal timing and dosage of rhGH treatment initiation in early life
iv. The effect of rhGH interruption at completion of growth
v. Effects of rhGH on behavior and cognitive function across the age range
vi. Impact of rhGH treatment on activities of daily living and well-being as defined by WHO
vii. Influence of IGF-I titration on clinical effects
viii. Effect of rhGH on glucose metabolism/diabetes risk, mainly long-term effect
ix. Effects of rhGH therapy on sleep and sleep-disordered breathing in PWS adults
x. RCTs investigating combination approaches to treatment

Additional areas for future research

xi. Effects of GH/IGF-I on nasopharyngeal tissue and mainly whether adenotonsillectomy changes the course or may avoid potential side effects of rhGH on sleep disorders and obstructive sleep apnea
xii. Dose-response relationships investigating efficacy of physiological (rather than pharmacological) dosing
xiii. Effects of rhGH treatment in children and adults on visceral adiposity and ectopic fat, eg, muscle, liver, and pancreas
xiv. Effects of rhGH on timing of development or severity of hyperphagia
xv. Effects of rhGH on bone maturation and premature pubarche
xvi. Effects on structural brain development
xvii. Scoliosis and slipped capital femoral epiphysis in children
xviii. Is there hypersensitivity to rhGH in PWS?
xix. Thyroid function before and after rhGH
xx. Effects on cardiac function
xxi. Effects of rhGH on lipid metabolism
xxii. Effects of rhGH on water retention
xxiii. Intracranial hypertension (difficult to assess in young children)

[a] All participants were asked to discuss areas for future investigation within breakout groups. All participants were then asked to order the areas, by priority, using a secret ballot.

apy, weight management therapy and behavioral therapy, ophthalmological and orthopedic interventions, and neurological, psychiatric, and endocrine care (replacement therapies for sex hormones, GH, L-thyroxine, cortisol). Although rhGH therapy is costly (92), compared with the cost of the provision of all of these services, the cost of rhGH may be relatively modest. However, a true understanding of the healthcare burden of treating individuals with PWS requires long-term health outcome research studies.

## Future Directions

At the end of the meeting, workshop participants were asked to individually rank, in order of importance, areas needing further research that had been discussed during breakout sessions. It is not surprising that continued surveillance of long-term effects of rhGH treatment was considered the top priority, particularly with regard to glucose metabolism and diabetes risk, as well as sleep and sleep-disordered breathing. The impact of rhGH treatment on quality of life, not only of patients but also of their families, was also ranked as an important aspect of treatment response that needs additional documentation. Most of the attendees who were not physicians saw an important place for future clinical trials combining rhGH with other therapeutic approaches, particularly those targeting hyperphagia and behavior. The top 10 areas that received the highest priority scores can be seen in Table 6.

## Conclusion

It is hoped that this PWS Workshop Summary will give patients, caregivers, and physicians a framework with which to optimize care. More importantly, it is hoped that it will help harmonize the healthcare access of the pediatric and adult populations with PWS, not just with regard to rhGH treatment but also with regard to the need for lifelong follow-up of these patients by multidisciplinary teams with experience in PWS. Finally, we stress the importance of the ethical framework in which healthcare specialists working with patients with PWS should practice and which should emphasize principles of informed consent/assent, respect for persons, and distributive justice.

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