

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Human Growth Hormone Treatment for Children with Prader-Willi Syndrome: A Review of Clinical Effectiveness, Cost- Effectiveness, and Guidelines

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Context and Policy Issues

Prader-Willi Syndrome (PWS) is a rare disorder with an incidence of approximately one in 15 000 to 30 000 births. The condition arises from various genetic disruptions of an imprinted region of chromosome 15 and was the first condition recognized as related to differential parental gene expression.^{1,2} Pediatric PWS patients typically present clinically with hypotonia (low muscle tone), diminished stature, mild dysmorphic facial features (e.g., narrow forehead, small upturned nose), hyperphagia (excessive appetite), hypogonadism, behavioral abnormalities, developmental delay, and endocrine disturbances including human growth hormone (hGH) deficiency.¹⁻³

hGH treatment for PWS patients improves body composition and motor development and is recommended in the 2013 PWS evidence-based consensus guidelines produced by the Growth Hormone Research Society.⁴ As a leading driver of medication costs for the pediatric PWS population, the discernment of additional treatment benefits of hGH may reduce its high incremental cost for PWS relative to quality of years gained.^{5,6}

Two previous CADTH reports examined the clinical effectiveness of hGH for PWS in adolescents and adults.^{7,8} These reports found that treatment with hGH results in improvement in body composition in patients with Prader-Willi syndrome and summarized evidence-based guidelines for the treatment of children and adults with PWS. The purpose of this report is to provide an update regarding the clinical effectiveness of hGH in pediatric PWS patients (0 to 19 years) and a summary of cost-effectiveness analyses and recent evidence-based guidelines.

Research Questions

1. What is the clinical effectiveness of human growth hormone treatment for children with Prader-Willi syndrome?
2. What is the cost-effectiveness of human growth hormone treatment for children with Prader-Willi syndrome?
3. What are the evidence-based guidelines regarding the use of human growth hormone treatment for children with Prader-Willi syndrome?

Key Findings

One small, high-quality randomized controlled trial, in addition to moderate quality evidence from four small randomized controlled trials, examining a total of 139 patients, and two cohort studies were identified on human growth hormone treatment of pediatric patients with Prader-Willi Syndrome. Improved body composition, behavioral benefits, and improved quality of life associated with human growth hormone treatment were suggested in the evidence. However, possibly due to small sample sizes, statistically significant treatment benefits were not consistently observed in the identified evidence. Inconsistent evidence for improved cognition was also identified, although the highest quality evidence suggested that, at least in patients with Prader-Willi Syndrome previously treated with human growth hormone until adult height was reached, no cognitive benefits manifested following one year of treatment. Significant uncertainty is therefore associated with the clinical

effectiveness evidence in this report. Data on adverse events and risks of human growth hormone treatment was absent from the identified evidence on this patient population. No cost-effectiveness evidence or relevant guidelines were identified in the limited literature search.

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Ovid Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2014 and December 13, 2017. Another search was done using the economic studies filter for English language documents published between January 1, 2012 and December 14, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. A second reviewer confirmed the final study selection. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Children (aged 0-19 years) with Prader-Willi syndrome
Intervention	Human growth hormone, or somatotropin. Trade names include: Genotropin, Saizen, Humatrope, Omnitrope, Nutropin, Norditropin
Comparator	No treatment or placebo, supportive care for symptoms or complications
Outcomes	<p>Q1: Clinical effectiveness and impact on symptoms (e.g., bone mineral density, cognitive and behavioural functioning, physical functioning and activity, weight and body composition, height, fertility, hypogonadism, obesity, hypotonia, diabetes risk, flexibility), safety, risks associated with treatment</p> <p>Q2: Cost-effectiveness outcomes (e.g., incremental cost per QALY or health benefit)</p> <p>Q3: Guidelines for the use of hGH in children with Prader-Willi, dosing guidelines for this population, types of patients who should not receive hGH, guidelines regarding the use of the GH stimulation test to determine eligibility for hGH treatment</p>
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, longitudinal observational studies with a control group, economic evaluations, evidence-based guidelines

hGH = human growth hormone; QALY = quality-adjusted life year.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, were published prior to 2012 (for economic studies) or prior to 2014 (for all other publications), or were previously evaluated in previous Rapid Response reports on this topic.^{7,8} In addition, guidelines with unclear methodology were excluded.

Critical Appraisal of Individual Studies

Randomized controlled trials (RCTs) and longitudinal observational studies were critically appraised using the Downs and Black checklist.⁹ Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 148 citations were identified in the literature search. Following screening of titles and abstracts, 113 citations were excluded and 35 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 33 publications were excluded for various reasons, while seven publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study characteristics of the included RCTs and observational studies are also summarized in Appendix 2, Table 2.

Study Design

The seven articles meeting the selection criteria consisted of two prospective comparative cohort studies, both published in 2017,^{2,6} and five RCTs.^{1,10-13} All five RCTs had a follow-up of two years.^{1,10-13} The observational studies observed one cohort with an average 4 year hGH treatment duration,² while the largest study evaluated patients who had received at least one year of hGH treatment.⁶

Country of Origin

Four RCTs were conducted in the Netherlands,^{1,10,11,13} and one in Sweden.¹² One cohort study was conducted in the USA,⁶ and one in Poland.²

Patient Population

The population of interest in these seven studies was pediatric patients diagnosed with PWS,^{1,2,6,10-13} and six of these studies mentioned that PWS was genetically confirmed in study participants.^{1,2,6,10,12,13} The largest study was a longitudinal observational study that enrolled 127 PWS patients, while the other included observational study examined a cohort of 36 patients.⁶ The largest RCT examined 47 PWS patients while the smallest RCT enrolled 19 PWS patients.¹² Studies of rare diseases like PWS often encounter challenges of small sample sizes.¹² None of the included studies used the GH stimulation test as part of the patient inclusion or exclusion criteria; however, Kuppens et al. administered an arginine-growth hormone releasing hormone stimulation test at the end of the two year study.¹³ This RCT examined patients (median age 17.8 years) that had received hGH during childhood for at least two years, had achieved adult height, and were currently on hGH.¹³

Interventions and Comparators

The RCTs specified the use of biosynthetic hGH (Genotropin; Pfizer Inc., New York, NY) delivered subcutaneously (s.q.).^{1,10-13} Three RCTs used a dose of 1.0 mg/m²/day,^{1,10,11} one RCT used a dose of 0.33mg/kg/day,¹² and one RCT used 0.67 mg/m²/day.¹³ The two prospective comparative studies did not include specific patient inclusion criteria for hGH treatment and the dose and brand of hGH were not reported in the observed treatment group.^{2,6} The RCTs all compared hGH treatment to pediatric PWS patients that received no hGH treatment. Two RCTs started hGH treatment in the control group after one year.^{11,12} One RCT included physical training for patients in both arms of the study however a description of frequency, duration, or type of physical training was not provided.¹¹ The latest RCT, Kuppens et al., compared hGH continuation with hGH cessation using a placebo in a double-blind crossover RCT.¹³ The observational longitudinal studies both used comparator PWS patients that did not receive hGH treatment, in addition to long term hGH treated patients,² no hGH treatment due to severe obesity,² as well as comparator groups of different ages of hGH treatment initiation (i.e., less than one year old, between one and two years old, and between three and five years old).⁶

Outcomes

Growth and Body Composition

Outcomes of growth and body composition were examined in six included studies.^{1,6,10-13} Height, weight, and body mass index (BMI) were reported in two RCTs,^{1,10} and one cohort study reported BMI alone.⁶ Body composition was measured by Dual Energy X-ray Absorptiometry in two RCTs.^{1,12} Muscle thickness, muscle strength, and motor performance were also reported in the identified evidence.¹¹

Behavioural Outcomes

One focus of the large comparative cohort study was behaviour.⁶ This study examined adaptive behaviour using the Vineland Adaptive Behavior standard, and the Repetitive Behavior Scale-Revised. Results of individual domains of the Vineland Adaptive Behavior standard (i.e., Communication, Daily Living Skills, Socialization) and the Adaptive Composite were reported (M = 100, SD = 15). The Repetitive Behavior Scale-Revised uses a four-point scale on 43 items in six subscales, a higher score indicated more problematic behaviors.⁶ Changes in different aspects of behaviour during and after hGH treatment were also evaluated by a parental questionnaire in the RCT by Bohm et al.¹²

Hyperphagia

Hyperphagia was examined in the largest RCT which reported total energy intake, fat percentage of energy intake, protein percentage of energy intake, and carbohydrate percentage of energy intake. This RCT also examined resting energy expenditure.¹ Hyperphagic behaviour (e.g., food seeking) was also examined using a questionnaire in one cohort study.⁶

Cognitive Outcomes

Cognition was a focus in four included studies.^{6,10,12,13} IQ was measured by the Kaufman Brief Intelligence Test-2 (K-BIT-2),⁶ Speedy Performance test of intelligence (SPIQ),¹² Wechsler Adult Intelligence Scale 3rd Edition,¹³ and Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) or Wechsler Intelligence Scale for Children-Revised (WISC-R).¹⁰ However, the RCT by Bakker et al.¹⁰ evaluated the relationship of IQ to health-

related quality of life (HRQoL) after hGH treatment and did not report this as a separate outcome. Additional assessments that had a cognitive component were reported by Bohm et al.¹² and Kuppens et al.¹³ which included Raven's Standard Progressive matrices test or Coloured Progressive Matrices,¹² Arthur's Adaptation of Leiter's Performance Scale,¹² Terman-Merrill scale of intelligence,¹² Bender Gestalt test,¹² Goodenough-Harris Draw-a-Man test,¹² Verbal IQ subtests (Vocabulary, Similarities, Arithmetic, Digit Span, Information and Comprehension)¹³ and Performance IQ subtests (Picture completion, Coding, Block design, Matrix Reasoning, Picture Arrangement).¹³

Health-Related Quality of Life

HRQoL was evaluated by one RCT.¹⁰ PWS patients completed the Dutch Children AZL/TNO Questionnaire Quality of Life short form (DUX25), and a PWS-specific questionnaire, the DUX Prader-Willi Syndrome (DUXPW).¹⁰ These HRQoL evaluations were comprised of four subdomains related to different aspects of daily functioning in children and adolescents: Physical, Home, Emotional, and Social functioning.¹⁰

Other Outcomes

Three studies reported blood test results.^{1,12,13} The effects of hGH on pediatric PWS patient blood serum levels of insulin-like growth factor 1 (IGF-1),^{12,13} glucose,¹ insulin,¹ and adiponectin¹ were reported.

One comparative cohort study focused on the clinical effectiveness of hGH for sleep-related breathing disorders in PWS patients.² Polysomnography studies (PSG) were conducted to assess respiratory flow, respiratory effort, and blood oxygen saturation (ODI) to calculate an apnoea-hypopnoea index (AHI). This study also reported the type of apnoea and oxygen desaturation characteristics in hGH treated and untreated PWS patients.²

Summary of Critical Appraisal

A tabulated summary of the strengths and limitations of the identified evidence is provided in Appendix 3, Table 3.

The five RCTs shared strengths of clearly defined outcomes, defined patient eligibility of age and confirmed PWS diagnosis, and provided a description of appropriate statistical methodology.^{1,10-13} Four RCTs also had a clearly defined intervention;¹⁰⁻¹³ however, Reus et al. failed to provide details on the physical training component of the intervention and comparator.¹¹ Reus et al. was the only RCT to provide a Consolidated Standards of Reporting Trials (CONSORT) diagram of patient recruitment;¹¹ one narratively described patient recruitment data,¹³ while the other RCTs did not provide any patient recruitment data.^{1,10,12} All RCTs provided tabulated patient characteristics, but Reus et al. also evaluated characteristics for baseline statistical differences.¹¹ While statistical assessment of differences between groups at baseline is not necessary according to the CONSORT statement,¹⁴ baseline differences between groups may contribute to statistically significant differences in the results, as observed for the assessments of DUXPW in the study by Bakker et al.¹⁰ Two RCTs were designed as open label trials, increasing potential for bias in patient and physician outcome assessment.^{1,12} The three blinded studies outlined the roles of blinded investigators, minimizing the potential for similar bias in assessments,^{10,11,13} one of which was double-blinded using a placebo injection as a control.¹³ A discussion of limitations of the trial was provided in three RCTs,¹¹⁻¹³ and randomization methodology was described in three RCTs.^{1,10,13}

One of the identified RCTs, Kuppens et al.,¹³ outlined methods for allocation concealment, provided a statistical power calculation, and mentioned adverse events; it was judged that this RCT had the fewest methodological quality limitations in the identified evidence. None of the RCTs however mentioned any potential issues of compliance.^{1,10-13} Three studies were industry funded studies,^{1,10,13} while two did not provide any statement regarding potential conflict of interests (COIs).^{11,12} Reus et al. described outcome assessments in the methodology for which the results were not reported other than a mention from the authors that the assessments were inconsistently applied to the trial participants.¹¹

The identified cohort studies both employed a prospective approach with defined outcomes.^{2,6} Dykens et al. also provided tabulated patient characteristics, determined statistical power, discussed the study limitations, and reported no COIs.⁶ Lecka-Ambroziak et al. described appropriate statistical methodology.² In addition to a lack of randomization these two studies were also limited by an open label design, statistically significant differences between patient groups where confounding was not addressed, a lack of patient recruitment data, undefined hGH treatment, no adverse event data, and no compliance information.^{2,6} Lecka-Ambroziak et al. did not provide a statistical power calculation, did not provide a statement regarding COIs, and enrolled a comparator group confounded by severe obesity.²

Summary of Findings

Key findings of the identified studies are summarized in Appendix 4, Table 4.

1. What is the clinical effectiveness of human growth hormone treatment for children with Prader-Willi syndrome?

Growth and Body Composition

Kuppens et al. found that both fat mass and lean body mass (LBM) demonstrated statistically significant deterioration upon cessation of hGH by substitution with placebo.¹³ Dykens et al. used multilevel regression models and estimated a statistically significant longitudinal benefit of hGH treatment of PWS patients of a lower BMI over longer term treatment of two to four years.⁶

In one RCT by Bakker et al.,¹ no statistically significant differences were observed between hGH-treated and untreated PWS patient groups in outcomes of BMI, or fat mass at one year. Additionally, infant PWS patients treated with hGH did not demonstrate a statistically significant difference compared to untreated PWS infants in outcomes of LBM. Similarly, treated and untreated pre-pubertal PWS patients were not observed to have statistically significant outcomes of resting energy expenditure (REE; a calculation based upon body composition and energy intake), or energy intake to REE ratio. It was not reported if this RCT was adequately powered to identify differences in these outcomes. This RCT did identify statistically significant differences in outcomes of height, skin fold tests, fat percentage between treated and untreated infants and pre-pubertal PWS patients favouring hGH treatment closer to standard deviation scores. Treated pre-pubertal PWS patients also had significantly more favourable outcomes of LBM as compared to untreated controls. Improved outcomes were observed in patients treated for two years and patients treated for one year at a double dose of hGH.¹

Reus et al.¹¹ examined the impact of hGH treatment of PWS patients on muscle thickness, muscle strength, and motor development and found statistically significantly increased muscle thickness in one of four muscle groups tested in hGH treated patients. Multilevel

regression models controlling for age and baseline muscle thickness identified a statistically significant hGH-dependent increase in muscle thickness for all four muscle groups as compared to control patients. The authors also suggested a benefit of physical training although no quantitative results or physical training methodology were presented.¹¹

Behavioural Outcomes

Cessation of hGH treatment for 6 months resulted in a statistically significant increase in behavioral issues as measured by parental questionnaire in the RCT by Bohm et al.¹² Vineland scales of Communication and Daily Living Skills but not Socialization were significantly improved with treatment when examined using multilevel regression models in the cohort study by Dykens et al.⁶ However, no statistically significant differences were observed between hGH treated and untreated PWS patients in the Repetitive Behavior Scale-Revised.⁶

Hyperphagia

Evidence from one RCT did not identify a statistically significant difference in total energy intake between hGH treated and untreated infant and pre-pubertal PWS patients. Statistically significant differences were also not identified between patient groups in outcomes of percentage of energy intake derived from dietary fat, carbohydrates, or protein.¹ A hyperphagia questionnaire did not reveal any statistically significant differences between treated and untreated PWS patients in Dykens et al.⁶

Cognitive Outcomes

Kuppens et al.¹³ and Bohm et al.¹² were not able to identify any statistically significant impacts of hGH treatment for pediatric PWS patients on cognitive outcomes using a wide variety of assessments. Bohm et al. suggested narratively that hGH treatment resulted in improved Bender test results, however no quantitative data is presented. It was not reported if this RCT had sufficient statistical power in order to observe differences between treatment groups.¹²

In contrast to the RCT by Bohm et al.,¹² the larger cohort study by Dykens et al.⁶ identified statistically significant improvements in some cognitive measures for hGH treated pediatric PWS patients. Verbal IQ and Composite IQ but not Nonverbal IQ as assessed by K-BIT-2 were significantly improved with hGH treatment. PWS patients initiated on hGH treatment at less than one year of age had a statistically significant improved Nonverbal IQ and Composite IQ as compared to PWS patients that initiated the same treatment between one and two years, and those patients that initiated treatment between three and five years. Multilevel regression models also indicated a statistically significant longitudinal improvement for the hGH treatment group in outcomes of Verbal and Composite IQ (K-BIT-2).⁶

Health-Related Quality of Life

Identified RCT evidence supported a statistically significant increase in HRQoL for PWS children treated with hGH as compared to untreated PWS children in the physical subdomain of the DUX25 assessment and in a disease-specific HRQoL assessment (DUXPW). The interpretation of the DUXPW increase was complicated by the appearance of baseline differences between groups.¹⁰

Other Outcomes

Kuppens et al. observed a statistically significant improvement in IGF-1 levels in hGH treated PWS patients.¹³ The RCT by Bohm et al.,¹² also documented statistically significant increases in IGF-1 levels at two years in hGH treated patients, which were also observed to be correlated with behavioral evaluations of irritation. No statistically significant differences in fasting levels of glucose and insulin were observed, however more favourable fasting levels of adiponectin were observed in hGH treated PWS patients as compared to controls in Bakker et al.¹

The cohort study examining the impact of hGH treatment on sleep-related breathing disorders did not identify any improved outcomes for PWS children. A statistically significant finding of increased ODI following short-term hGH therapy was observed, predicting less quality sleep for these patients.²

2. What is the cost-effectiveness of human growth hormone treatment for children with Prader-Willi syndrome?

No evidence of hGH cost-effectiveness for PWS treatment was identified.

3. What are the evidence-based guidelines regarding the use of human growth hormone treatment for children with Prader-Willi syndrome?

No guidelines meeting the selection criteria were identified.

Limitations

Most of the clinical effectiveness evidence presented in this report was from five small RCTs, four of which had unreported statistical power. There was no information on adverse events and compliance in the identified evidence which prevented a conclusion regarding the benefits of hGH therapy compared to the risks for PWS patients under 19 years old. This report is also limited by a lack of identified evidence on cost-effectiveness produced within the past five years and a lack of identified evidence-based guidelines produced since the completion of previous Rapid Response reports.^{7,8}

Conclusions and Implications for Decision or Policy Making

The findings from this report do not contradict previous Rapid Response reports examining hGH treatment of PWS patients; however, a greater degree of uncertainty is associated with the findings identified here. One small RCT with minor limitations, moderate quality evidence from four small RCTs, and two cohort studies were identified. The prior Rapid Response reports identified more clinical effectiveness evidence than presented here; however, the population of interest was adolescent and adult patients.^{7,8}

The evidence identified in this report is not consistent with regard to the clinical effectiveness of hGH treatment of children with PWS. Consistent evidence for growth and body composition benefits of hGH treatment was not identified.^{1,6,10,11,13} The highest quality RCT from Kuppens et al. reported improved LBM and fat mass for hGH treated PWS patients over one year.¹³ One cohort study found that treatment was associated with lower BMIs,⁶ while one underpowered RCT did not find a statistically significant effect of treatment on BMIs.¹ One RCT reported that a higher BMI was associated with a lower HRQoL; however, the authors did not report an impact of hGH treatment on BMI.¹⁰ Improvements in height,¹ body composition (fat percentage and LBM),¹ and muscle mass,¹¹

were identified in two small RCTs. Total energy intake did not significantly change with treatment in one small RCT,¹ and a larger cohort study found no statistically significant differences in a questionnaire that measured hyperphagic behaviour.⁶ However, behavioral benefits were observed in domains of communication and daily living in this study.⁶ Additionally, six month cessation of hGH treatment resulted in a statistically significant increase in negative behavioral issues associated with PWS.¹² The impact of hGH treatment for pediatric PWS patients on cognition was mixed with one larger study finding IQ benefits of treatment including a statistically more pronounced effect when treatment was initiated before the age of one year,⁶ while one small RCT was unable to detect any cognitive benefits using a variety of assessments.¹² A well conducted RCT also did not identify any benefits of hGH on a variety of cognition assessments in young PWS patients of adult height.¹³ Results of one small RCT suggested increased HRQoL for PWS children receiving hGH treatment.¹⁰ Blood serum levels of IGF-1 increased with hGH treatment in two RCTs,^{12,13} and decreased IGF-1 levels correlated with increased behavioral issues upon treatment cessation in one of these small RCTs.¹² Levels of glucose and insulin were not significantly changed with treatment; however, a statistically significant increase in adiponectin levels of pre-pubertal PWS patients receiving hGH was observed in one study.¹ No detectable impact on sleep related breathing disorders was observed for hGH treated PWS children.²

No cost-effectiveness evidence published since 2012 or relevant guidelines published since 2014 on the use of hGH in pediatric PWS patients were identified. The guidelines referenced in the included evidence were published in 2013,⁴ and summarized in a previously published CADTH Rapid Response report.⁷ These guidelines recommend that hGH treatment be considered following PWS diagnosis including in adult, children, and infants, and provide recommended doses for hGH therapy. An older cost-effectiveness study was also cited in one included study and reportedly identified a high incremental cost per quality adjusted life year (QALY) for hGH treatment of PWS.^{6,15}

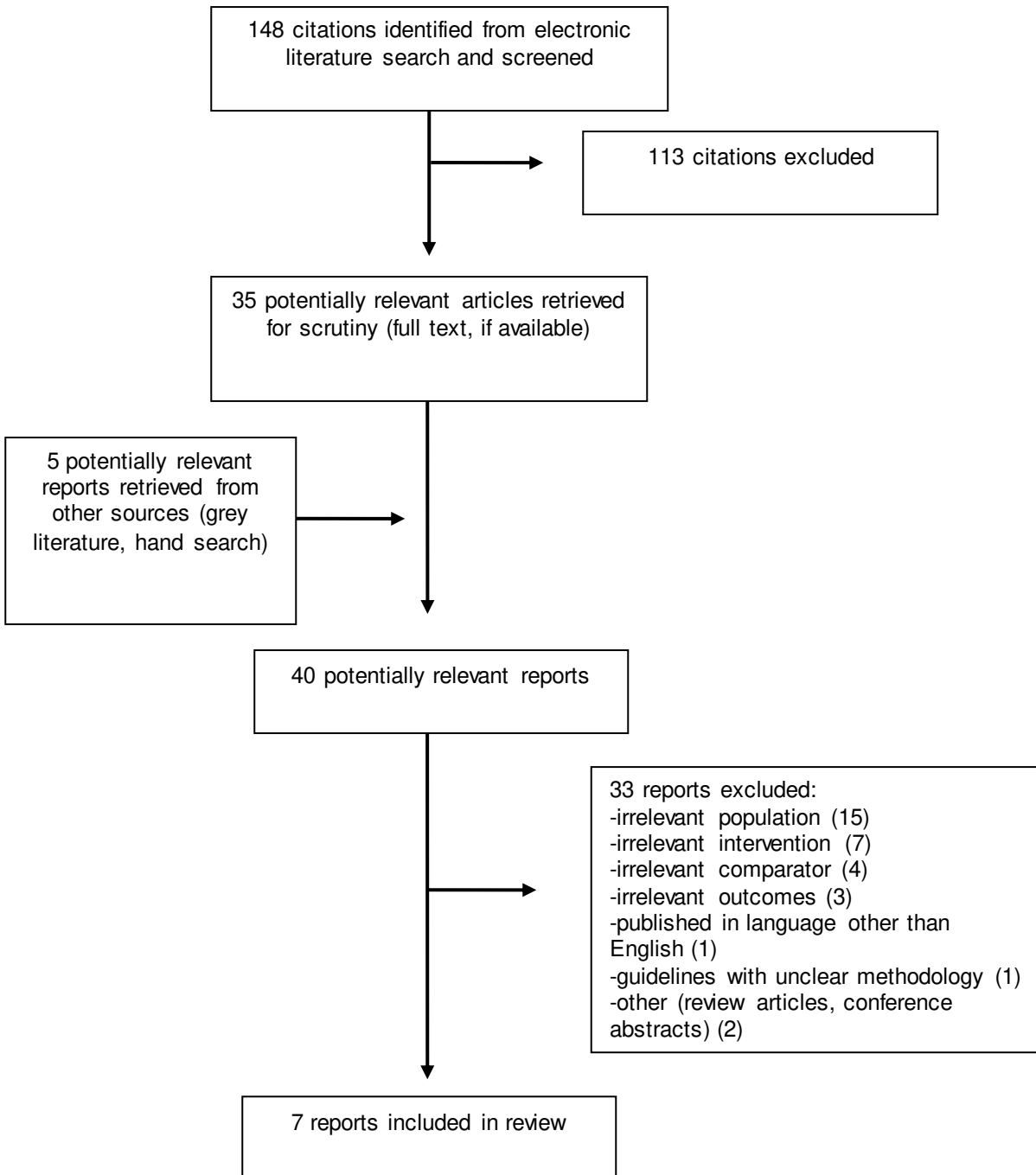
Collectively the identified evidence, published since 2014, presented limited clinical effectiveness data supportive of hGH for pediatric PWS patients for a variety of outcomes. Adverse event data was completely absent from the identified evidence, therefore assessment of benefits and risks were not possible. A lack of detectable differences between treatment groups in the evidence identified in this report is associated with significant uncertainty as four RCTs were likely underpowered. The clinical significance of the observed advantages of hGH treatment was not discussed by study authors. As suggested by authors of one included study, additional RCT evidence may not be forthcoming as such study proposals may be determined to be unethical as hGH is now a recommended treatment for this patient group.⁶

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Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Clinical Studies

Author, Publication Date, Country	Study Design, duration	Patient characteristics	Intervention	Comparator(s)	Outcomes
Lecka-Ambroziak et al., 2017² Poland	Comparative cohort; Average 4 year hGH therapy for one study group	PWS (genetically verified) Age: short-term treatment group average age 2.5 years, long-term treatment group average age 8.8 years (n = 36)	rhGH treatment	<ul style="list-style-type: none"> • Patients prior to rhGH treatment • longer term rhGH treated patients (average 4 years) • No rhGH treatment due to severe obesity 	SRBD as measured by: <ul style="list-style-type: none"> • AHI (correlated with desaturation) • Blood oxygen saturation (ODI) • Type of apnoea
Dykens et al., 2017⁶ USA	Comparative cohort; At least one year hGH treatment	PWS (genetically verified) Age: 4 - 21 years (n = 127)	Growth Hormone Therapy (GHT)	<ul style="list-style-type: none"> • Groups based upon age of GHT initiation • Patients naive to GHT 	<ul style="list-style-type: none"> • IQ (K-BIT-2) • Adaptive behavior (Vineland Adaptive Behavior standard) • Hyperphagia Questionnaire • Repetitive Behavior Scale-Revised • BMI
Kuppens et al., 2016¹³ The Netherlands	RCT: Cross-over of 1 year hGH treatment 2 year total follow-up	PWS (genetically verified) Age: Median = 17.8 years (range = 15.6 to 19.4 years)	0.67 mg/m ² /day s.q. Biosynthetic hGH (Genotropin; Pfizer Inc., New York, NY)	Placebo	<ul style="list-style-type: none"> • IQ (WAIS-III) • VIQ - Vocabulary, Similarities, Arithmetic, Digit Span, Information and Comprehension • PIQ - Picture Completion, Coding, Block design, Matrix Reasoning and Picture Arrangement • Fat mass • LBM • IGF-1
Bakker et al., 2015¹⁰ The Netherlands	RCT; 2 year follow-up both groups, 11 year follow-up of treated patients (no comparator)	PWS (genetically verified) Age: Females 6 - 12 years, Males 6 - 14 years (RCT group = 26)	1.0mg/m ² /days.q. Biosynthetic hGH (Genotropin; Pfizer Inc., New York, NY)	No hGH treatment	<ul style="list-style-type: none"> • HRQoL (DUX25 and DUXPW) • Height, weight, BMI • Cognition (IQ as measured by WPPSI-R or WISC-R)
Bakker et al.,	RCT; 2 year follow-up	PWS (genetically verified)	1.0mg/m ² /days.q. Biosynthetic hGH	No hGH treatment (one year for	<ul style="list-style-type: none"> • Energy Intake (%fat, % protein, %

Author, Publication Date, Country	Study Design, duration	Patient characteristics	Intervention	Comparator(s)	Outcomes
2015¹ The Netherlands		Age: Females 6 months - 12 years, Males 6 months - 14 years No signs of puberty Patients divided into infants (<3.5 years) and pre-pubertal (≥3.5 years) (n = 47)	(Genotropin; Pfizer Inc., New York, NY)	infants, two years for pre-pubertal patients)	carbohydrate) • Height, weight, BMI • Body composition • Resting Energy Expenditure • Blood serum levels of Insulin, Glucose, IGF-1, and adiponectin
Reus et al., 2014¹¹ The Netherlands	RCT; 2 year follow-up	PWS Age: < 36 months (n = 22)	1.0mg/m ² /days.q. Biosynthetic hGH (Genotropin; Pfizer Inc., New York, NY) with physical training	No hGH treatment with physical training	• Weight adjusted muscle thickness • Weight adjusted muscle echo intensity (ultrasound) • Muscle strength (IMS) • Motor performance (GMFM)
Bohm et al., 2014¹² Sweden	RCT; 2 year follow up	PWS (genetically verified) Age: Mean 2.5 years (n = 19)	0.033 mg/kg/day s.q. Biosynthetic hGH (Genotropin; Pfizer Inc., New York, NY for two years, followed by six months no treatment	No hGH treatment for one year, double hGH dose in second year, followed by six months no treatment	• Cognition (Raven's Standard Progressive matrices test or Coloured Progressive Matrices, Arthur's Adaptation of Leiter's Performance Scale, Terman-Merrill scale of intelligence, SPIQ test) • Bender Gestalt test • Goodenough-Harris Draw-a-Man test • Parental questionnaire • Blood serum IGF-1 levels • Body composition

AHI = apnoea-hypopnoea index; DUX25 = Dutch Children AZL/TNO Questionnaire Quality of Life short form; DUXPW = DUX Prader-Willi; GMFM = Gross Motor Function Measurement; hGH = human growth hormone; HRQoL = health-related quality of life; IGF-1 = insulin-like growth factor 1; IMS = infant muscle strength; IQ = intelligence quotient; K-BIT-2 = Kaufman Brief Intelligence Test-2; PWS = Prader-Willi Syndrome; RCT = randomized controlled trial; rhGH = recombinant human growth hormone; SPIQ = Speedy Performance test of Intelligence; s.q. = subcutaneous; SRBD = sleep-related breathing disorders; WAIS -III = Wechsler Adult Intelligence Scale 3rd Edition; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised; WISC-R = Wechsler Intelligence Scale for Children-Revised.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black Checklist⁹

Strengths	Limitations
Lecka-Ambroziak et al., 2017 ^c	
<ul style="list-style-type: none"> • Statistical methods described • Defined outcomes 	<ul style="list-style-type: none"> • Non-randomized study • No statistical power calculation to determine sample size - small study • Open label study • Baseline patient characteristics contain significant differences • No patient recruitment data • Some before and after design • Intervention not clearly defined • No adverse event reporting • No compliance data • No COI statement • No discussion of study limitations • Confounding of severe obesity in comparator group
Dykens et al., 2017 ^b	
<ul style="list-style-type: none"> • Patient characteristics tabulated • Defined outcomes • Statistical power determined a priori • Discussion on study limitations provided • Statement of no COIs 	<ul style="list-style-type: none"> • Non-randomized study • Open label study • Unclear differential enrollment into three outcome assessment groups • Intervention not clearly defined • Baseline patient characteristics contain statistically significant differences • Statistical methodology not provided • No patient recruitment data • Intervention not clearly defined • No adverse event reporting • No compliance data
Kuppens et al., 2016 ¹³	
<ul style="list-style-type: none"> • Randomization methodology described • Allocation concealment methodology not described • Role of blinded investigators outlined • Double-blinded study • Clearly defined outcomes • Clearly defined intervention • Clearly defined patient eligibility • Statistical methods described • Patient characteristics tabulated • Patient recruitment data provided • Some discussion of study limitations • Statistical power calculation • Adverse event observation methodology mentioned 	<ul style="list-style-type: none"> • Adverse Event results not mentioned • Industry funded study • No compliance data
Bakker et al., 2015 ¹⁰	
<ul style="list-style-type: none"> • Randomization methodology described • Role of blinded investigators outlined • Clearly defined outcomes • Clearly defined intervention • Clearly defined patient eligibility 	<ul style="list-style-type: none"> • Patient characteristics not evaluated for significant differences • Allocation concealment methodology not described • No patient recruitment data • No statistical power calculation to determine sample size • No adverse event reporting

Strengths	Limitations
<ul style="list-style-type: none"> • Statistical methods described 	<ul style="list-style-type: none"> • No discussion of study limitations • Industry funded study • No compliance data
Bakker et al., 2015 ¹	
<ul style="list-style-type: none"> • Randomization methodology described • Clearly defined outcomes • Clearly defined intervention • Clearly defined patient eligibility • Statistical methods described 	<ul style="list-style-type: none"> • Patient characteristics not evaluated for significant differences • Allocation concealment methodology not described • Open label study • No patient recruitment data • No statistical power calculation to determine sample size • No adverse event reporting • No discussion of study limitations • Industry funded study • No compliance data
Reus et al., 2014 ¹¹	
<ul style="list-style-type: none"> • CONSORT diagram for patient recruitment/enrollment • Patient characteristics tabulated - no statistically significant differences between groups • Statistical methods described • Role of blinded investigators outlined • Defined patient eligibility • Clearly defined outcomes • Discussion on study limitations 	<ul style="list-style-type: none"> • Allocation concealment methodology not described • Randomization methodology not described • No adverse event reporting • No COI statement • No compliance data • No statistical power calculation to determine sample size • Inconsistent outcome assessment • Lack details of intervention
Bohm et al., 2014 ¹⁴	
<ul style="list-style-type: none"> • Patient characteristics tabulated • Statistical methods described • Defined patient eligibility • Clearly defined intervention • Clearly defined outcomes • Comprehensive discussion on study limitations 	<ul style="list-style-type: none"> • Allocation concealment methodology not described • Open label study • Randomization methodology not described • No patient recruitment data • No compliance data • No COI statement • No statistical power calculation to determine sample size • Inconsistent outcome assessment

COI = conflict of interest; CONSORT = Consolidated Standards of Reporting Trials.

Appendix 4: Main Study Findings and Author’s Conclusions

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author’s Conclusion
Lecka-Ambroziak et al., 2017 ^c	
<p><u>AHI Mean (± SD)</u> Prior to hGH (n = 11) 10.2 (± 6.9) Following hGH (n = 6) 12.0 (± 5.8) Long-term hGH (n = 17) 9.0 (± 6.5) No hGH (n = 8) 8.2 (± 5.4)</p> <p><u>AI Mean (± SD)</u> Prior to hGH (n = 11) 6 (± 4.5) Following hGH (n = 6) 9.1 (± 4.7) Long-term hGH (n = 17) 6.5 (± 5.7) No hGH (n = 8) 3.4 (± 2.2)</p> <p><u>HI Mean (± SD)</u> Prior to hGH (n = 11) 4.2 (± 2.9) Following hGH (n = 6) 2.9 (± 2.5) Long-term hGH (n = 17) 2.5 (± 1.6) No hGH (n = 8) 4.8 (± 3.5)</p> <p><u>CA Mean (± SD)</u> Prior to hGH (n = 11) 2.4 (± 3.1) Following hGH (n = 6) 4.8 (± 2.9) Long-term hGH (n = 17) 3.1 (± 4.4) No hGH (n = 8) 0.9 (± 0.5)</p> <p><u>OSA Mean (± SD)</u> Prior to hGH (n = 11) 2.3 (± 1.2) Following hGH (n = 6) 2.7 (± 1.7) Long-term hGH (n = 17) 2.5 (± 2.0) No hGH (n = 8) 2.0 (± 1.7)</p> <p><u>Mixed apnoea index Mean (± SD)</u> Prior to hGH (n = 11) 1.3 (± 1.2) Following hGH (n = 6) 1.6 (± 1.8) Long-term hGH (n = 17) 0.9 (± 0.8) No hGH (n = 8) 0.4 (± 0.3)</p> <p><u>ODI Mean (± SD)</u> Prior to hGH (n = 11) 36.3 (± 19.2) Following hGH (n = 6) 60.9 (± 25.4) Long-term hGH (n = 17) 25.1 (± 17.4) No hGH (n = 8) 22.0 (± 13)</p>	<p>“Our study confirms the high frequency of SRBD among PWS patients, mostly of moderate or severe type.” (pp. 680)</p> <p>“In conclusion, the results do not show a simple dependence between the SRBD and the period of rhGH therapy.” (pp. 680)</p> <p>“... we did not find the statistical differences between AHI values in relation to rhGH treatment. Moreover, the worsening of ODI found in our group of short-term rhGH therapy was not strictly related to SRBD.” (pp. 680)</p>
Dykens et al., 2017 ^b	
<p><u>K-BIT-2 Verbal IQ Mean (± SD) (P < 0.01)</u> hGH (n = 64) 81.64 (± 15.65) no hGH (n = 32) 67.54 (± 13.60)</p> <p><u>K-BIT-2 Nonverbal IQ Mean (± SD) (P > 0.05)</u></p>	<p>“Continuously treated versus untreated children maintained their advantages over time in Verbal and Full Scale IQ scores, and in their adaptive Communication and Daily Living Skills.” (pp. 71)</p> <p>“A potential boost in cognitive or adaptive functioning, however,</p>

Main Study Findings	Author's Conclusion
hGH (n = 64) 72.40 (± 17.50) no hGH (n = 32) 63.83 (± 18.11)	highlights the need to revisit previous justifications for GHT in PWS based solely on linear growth or body composition.” (pp. 71) “Cognitive and adaptive advantages should be considered an ancillary benefit and additional justification for GHT in people with PWS. Future efforts need to target apparent socioeconomic inequities in accessing GHT in the PWS population.” (pp. 64)
<u>K-BIT-2 Composite IQ Mean (± SD) (P < 0.01)</u>	
hGH (n = 64) 74.57 (± 16.44) no hGH (n = 32) 62.31 (± 15.30)	
<u>Vineland scales Communication Mean (± SD) (P < 0.05)</u>	
hGH (n = 64) 79.57 (± 14.12) no hGH (n = 32) 65.05 (± 17.31)	
<u>Vineland scales Daily Living Skills Mean (± SD) (P < 0.05)</u>	
hGH (n = 64) 74.57 (± 16.44) no hGH (n = 32) 62.31 (± 15.30)	
<u>Vineland scales Socialization Mean (± SD) (P > 0.05)</u>	
hGH (n = 64) 76.83 (± 16.81) no hGH (n = 32) 64.17 (± 14.82)	
<u>Hyperphagia Questionnaire Mean (± SD) (P > 0.05)</u>	
hGH (n = 64) 15.99 (± 3.30) no hGH (n = 32) 17.93 (± 2.79)	
<u>Repetitive Behavior Scale-Revised Mean (± SD) (P > 0.05)</u>	
hGH (n = 64) 36.63 (± 16.26) no hGH (n = 32) 42.11 (± 18.79)	
<u>K-BIT-2 Verbal IQ Mean (± SD) (P > 0.05)*</u>	
< 1 year start hGH (n = 38) 85.61 (± 14.81) 1-2 years start hGH (n = 42) 79.57 (± 15.80) 3-5 years start hGH (n = 34) 81.03 (± 13.08)	
* Current age of groups differs (P < 0.01)	
<u>K-BIT-2 Nonverbal IQ Mean (± SD) (P < 0.01)*</u>	
< 1 year start hGH (n = 38) 79.86 (± 13.87) 1-2 years start hGH (n = 42) 67.92 (± 15.66) 3-5 years start hGH (n = 34) 69.41 (± 14.87)	
* Current age of groups differs (P < 0.01)	
<u>K-BIT-2 IQ Composite Mean (± SD) (P < 0.01)*</u>	
< 1 year start hGH (n = 38) 82.58 (± 14.81) 1-2 years start hGH (n = 42) 70.55 (± 15.11) 3-5 years start hGH (n = 34) 72.09 (± 13.47)	
* Current age of groups differs (P < 0.01)	
<u>BMI Mean (± SD) (P > 0.05)*</u>	
< 1 year start hGH (n = 38) 18.45 (± 3.63) 1-2 years start hGH (n = 42) 20.43 (± 4.04) 3-5 years start hGH (n = 34) 22.11 (± 6.99)	
* Current age of groups differs (P < 0.01)	
Multilevel regression models indicated a statistically significant longitudinal impact of hGH on Verbal and Full Scale IQ, Daily Living, Communication Skills, and lower BMIs.	

Main Study Findings	Author's Conclusion																								
Kuppens et al., 2016 ¹⁰																									
<p>No statistically significant differences in IQ were observed in either crossover group between GH treatment period and placebo period in any measured IQ outcome.</p> <p><u>Fat Mass % (Range) (P = 0.002)</u></p> <table border="0"> <tr> <td>Placebo/GH 1 year placebo (n = 12)</td> <td>45.3 (38.2, 48.3)</td> </tr> <tr> <td>Placebo/GH 1 year GH (n = 12)</td> <td>41.7 (30.6, 50.6)</td> </tr> <tr> <td>GH/Placebo 1 year placebo (n = 13)</td> <td>44.1 (38.4, 52.3)</td> </tr> <tr> <td>GH/Placebo 1 year GH (n = 13)</td> <td>39.3 (33.2, 49.8)*</td> </tr> </table> <p><u>LBM kg (Range) (P = 0.008)</u></p> <table border="0"> <tr> <td>Placebo/GH 1 year placebo (n = 12)</td> <td>32.3 (30.6, 45.1)</td> </tr> <tr> <td>Placebo/GH 1 year GH (n = 12)</td> <td>34.6 (31.6, 44.0)*</td> </tr> <tr> <td>GH/Placebo 1 year placebo (n = 13)</td> <td>36.7 (31.5, 39.2)</td> </tr> <tr> <td>GH/Placebo 1 year GH (n = 13)</td> <td>35.1 (32.6, 41.3)</td> </tr> </table> <p><u>IGF-1 SDS (Range) (P < 0.001)</u></p> <table border="0"> <tr> <td>Placebo/GH 1 year placebo (n = 12)</td> <td>-0.4 (-0.9, -0.3)</td> </tr> <tr> <td>Placebo/GH 1 year GH (n = 12)</td> <td>2.1 (0.0, 2.4)*</td> </tr> <tr> <td>GH/Placebo 1 year placebo (n = 13)</td> <td>-0.7 (-1.7, 0.3)</td> </tr> <tr> <td>GH/Placebo 1 year GH (n = 13)</td> <td>1.8 (1.5, 2.4)*</td> </tr> </table> <p>*within group P < 0.05</p>	Placebo/GH 1 year placebo (n = 12)	45.3 (38.2, 48.3)	Placebo/GH 1 year GH (n = 12)	41.7 (30.6, 50.6)	GH/Placebo 1 year placebo (n = 13)	44.1 (38.4, 52.3)	GH/Placebo 1 year GH (n = 13)	39.3 (33.2, 49.8)*	Placebo/GH 1 year placebo (n = 12)	32.3 (30.6, 45.1)	Placebo/GH 1 year GH (n = 12)	34.6 (31.6, 44.0)*	GH/Placebo 1 year placebo (n = 13)	36.7 (31.5, 39.2)	GH/Placebo 1 year GH (n = 13)	35.1 (32.6, 41.3)	Placebo/GH 1 year placebo (n = 12)	-0.4 (-0.9, -0.3)	Placebo/GH 1 year GH (n = 12)	2.1 (0.0, 2.4)*	GH/Placebo 1 year placebo (n = 13)	-0.7 (-1.7, 0.3)	GH/Placebo 1 year GH (n = 13)	1.8 (1.5, 2.4)*	<p>“In conclusion, this cross-over trial in young adults with PWS who were treated for many years with GH during childhood shows that compared to GH treatment, 1 year of placebo did not deteriorate cognitive functioning. However, patients with a lower cognitive functioning had more loss in IQ points during placebo versus GH treatment. The reassuring finding that 1 year of placebo does not deteriorate cognitive functioning does, however, not exclude a gradual deterioration of cognitive functioning on the long term.” (pp. 7)</p> <p>“We now found no difference in cognition between those with a deletion versus mUPD + ICD, which suggests that long-term GH treatment during childhood improved cognitive functioning, particularly of those with mUPD + ICD.” (pp. 6)</p> <p><u>GH stimulation test</u></p> <p>“After the 2-year study, twenty-three young adults underwent an arginine-[growth hormone releasing hormone] test. Only 3 (13%) had a GH peak below the BMI-dependent cut-off. There was no significant influence of the GH peak on the effects of placebo versus GH administration on [total]IQ, [verbal]IQ or [performance]IQ (p > 0.604).” (pp. 6)</p>
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Bakker et al., 2015 ¹⁰																									
<p><u>Data was only provided graphically</u></p> <p>hGH treatment (n = 15) resulted in statistically significant improvements in HRQoL Physical subdomain of DUX25 (P < 0.05) and DUXPW (P < 0.001) as compared to untreated controls (n = 11) over two years. Other components of DUX25 (home, emotional, and social) did not demonstrate a statistically significant difference over two years.</p> <p>While some baseline characteristics were statistically evaluated, it was not clear if significant differences in HRQoL measures existed at baseline between treated and untreated groups. The graphical representation of DUXPW results suggested there was a baseline difference for this outcome.</p> <p>The long-term follow-up component of the study did not have a comparator.</p>	<p>“Our study shows that children with PWS report a normal HRQoL. Both children and parents indicated improvement in HRQoL during GH treatment, while this progression was not found in the randomly assigned untreated children with PWS.” (pp. 238)</p> <p>“According to children and parents, HRQoL improved in GH-treated children with PWS, while it decreased or remained similar to baseline in untreated controls with PWS.” (pp. 237)</p>																								
Bakker et al., 2015 ¹																									
<p><u>Infant Energy Intake change (kcal/day) at one year - Median (IQR) (P = 0.072)</u></p> <table border="0"> <tr> <td>hGH (n = 11)</td> <td>264 (135, 370)</td> </tr> <tr> <td>no hGH (n = 8)</td> <td>108 (7, 193)</td> </tr> </table> <p><u>Pre-pubertal Energy Intake change (kcal/day) at two years - Median (IQR) (P = NS)</u></p> <table border="0"> <tr> <td>hGH (n = 12)</td> <td>158 (-77, 371)</td> </tr> <tr> <td>no hGH (n = 16)</td> <td>-25 (-98, 189)</td> </tr> </table>	hGH (n = 11)	264 (135, 370)	no hGH (n = 8)	108 (7, 193)	hGH (n = 12)	158 (-77, 371)	no hGH (n = 16)	-25 (-98, 189)	<p>“In conclusion, children with PWS have a low to very low energy intake compared to daily energy requirements for age- and sex-matched children. In infants aged <3.5 years, energy intake increased during GH treatment compared to baseline, but it was not significantly different from the untreated ones. In pre-pubertal children, aged ≥ 3.5 years, energy intake did not significantly increase. In contrast to the energy intake, the children had a significant decrease in fat percentage and an increase in adiponectin levels, suggesting a protective effect of</p>																
hGH (n = 11)	264 (135, 370)																								
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Main Study Findings	Author's Conclusion
<p><u>Infant Height SDS at one year - Median (IQR) (P < 0.05)</u> hGH (n = 11) -1.1 (-2.0, -0.2) no hGH (n = 8) -2.3 (-3.4, -1.5)</p>	<p>GH treatment with regard to the development of obesity and diabetes mellitus type II development in infants and children with PWS. The focus of attention for parents to keep energy balance is to stimulate physical activity.” (pp. 329)</p> <p>“GH treatment was associated with a slight increase in energy intake, but also improved body composition and adiponectin levels, which suggests a protective effect of GH treatment.” (pp. 321)</p>
<p><u>Infant Sum of 4 SFs SDS at one year - Median (IQR) (P = 0.05)</u> hGH (n = 11) 0.9 (-1.1, 3.1) no hGH (n = 8) 4.0 (3.1, 5.3)</p>	
<p><u>Infant Fat percentage at one year - Median (IQR) (P = 0.05)</u> hGH (n = 11) 26.3 (15.2, 28.6) no hGH (n = 8) 36.1 (23.9, 40.9)</p>	
<p><u>No statistically significant differences observed following one year of hGH in infants as compared to controls in outcomes of:</u> <u>Fat, protein, or carbohydrate % of energy intake</u> <u>BMI SDS</u> <u>BMI PWS SDS</u> <u>Fat mass</u> <u>LBM</u> <u>Fasting levels of insulin or glucose</u></p>	
<p><u>Pre-pubertal Height at two years -Median (IQR) (P < 0.001)</u> hGH (n = 12) -0.2 (-0.4, 0.4) no hGH (n = 16) -1.7 (-2.4, -1.4)</p>	
<p><u>Pre-pubertal Sum of 4 SFs SDS at two years -Median (IQR) (P < 0.01)</u> hGH (n = 12) 1.6 (1.0, 3.3) no hGH (n = 16) 4.9 (2.8, 7.0)</p>	
<p><u>Pre-pubertal Fat percentage at two years -Median (IQR) (P < 0.05)</u> hGH (n = 12) 34.3 (21.5, 40.5) no hGH (n = 16) 39.4 (38.0, 45.1)</p>	
<p><u>Pre-pubertal Fat percentage SDS at two years -Median (IQR) (P < 0.05)</u> hGH (n = 12) 2.2 (1.4, 2.5) no hGH (n = 16) 2.6 (2.4, 2.8)</p>	
<p><u>Pre-pubertal LBM at two years -Median (IQR) (P = 0.001)</u> hGH (n = 12) 20.4 (17.8, 26.9) no hGH (n = 16) 14.4 (13.1, 16.5)</p>	
<p><u>Pre-pubertal LBM SDS at two years -Median (IQR) (P < 0.001)</u> hGH (n = 12) -1.3 (-1.6, -1.2) no hGH (n = 16) -3.0 (-3.2, -2.4)</p>	
<p><u>Pre-pubertal Adiponectin change (mg/L) at two years - Median (IQR) (P < 0.05)</u> hGH (n = 12) 2.8 (1.1, 3.6) no hGH (n = 16) -1.2 (-2.6, 1.0)</p>	

Main Study Findings	Author's Conclusion
<p>Reus et al., 2014¹¹</p>	
<p>No statistically significant differences observed following two years of hGH in pre-pubertal PWS patients as compared to controls in outcomes of: <u>Fat, protein, or carbohydrate % of energy intake</u> <u>BMI SDS</u> <u>BMI PWS SDS</u> <u>Fat mass</u> <u>Fasting levels of insulin, or glucose</u> <u>REE</u> <u>Energy intake to REE ratio</u></p> <p>Biceps brachii Muscle thickness SDS Mean (± SD) (P = NS) hGH (n = 10) -0.5 (± 1.7)* no hGH (n = 12) -1.4 (± 0.8) * statistically significant increase over baseline</p> <p>Forearm flexors Muscle thickness SDS Mean (± SD) (P < 0.05) hGH (n = 10) -0.5 (± 0.9)* no hGH (n = 12) -1.3 (± 0.8) * statistically significant increase over baseline</p> <p>Quadriceps Muscle thickness SDS Mean (± SD) (P = NS) hGH (n = 10) -0.9 (± 1.4) no hGH (n = 12) -1.4 (± 0.9)</p> <p>Tibialis anterior Muscle thickness SDS Mean (± SD) (P = NS) hGH (n = 10) -0.6 (± 1.1)* no hGH (n = 12) -0.8 (± 0.6) * statistically significant increase over baseline</p> <p>Multilevel regression models indicated a statistically significant longitudinal impact of hGH, as compared to controls, for all four muscle groups when controlled for age and baseline muscle thickness. This analysis found the effect to be independent of the age at which hGH treatment was initiated.</p>	<p>“GH increased muscle thickness, which was related to muscle strength and motor development in infants with PWS. Catch-up growth was faster in muscles that are most frequently used in early development. Because this effect was independent of GH, it suggests a training effect.” (pp. 1619)</p>
<p>Bohm et al., 2014¹²</p>	
<p>Data was only provided graphically</p> <p>Cognitive outcomes No significant cognitive or differences in any assessments between hGH treated (n = 10), and untreated controls (n = 9) at one year, or at two years where untreated controls had received double hGH dosing for the second year.</p> <p>IGF-1 levels A statistically significant increase in IGF-1 levels was observed in PWS patients receiving hGH. (P < 0.01) IGF-1 levels underwent rapid reduction following withdrawal of hGH. (P = 0.01)</p>	<p>“We believe this is the first study to show that abrupt-ceasing growth hormone treatment led to a successive deterioration in behavioural problems in children with Prader- Willi syndrome.” (pp. 59)</p> <p>“Contrary to our hypotheses, Group A’s cognitive skills did not improve as a result of GH treatment during year 1 and neither group exhibited improved cognitive levels relative to age norms during treatment. But as predicted, we found no significant difference in global cognition between the groups after 2 years of GH treatment. No other cognitive improvements were found as a result of GH therapy, either between or within the two groups, with the exception of better Bender test results in Group</p>

Main Study Findings	Author's Conclusion
<p>A correlation between IGF-1 levels and one behavioral factor (irritated) were observed at 30 months. ($P = 0.007$).</p> <p>Body composition Body composition results not reported.</p>	<p>A after the end of the treatment period.” (pp. 65)</p>

AHI = apnoea-hypopnoea index; AI = apnoea index; CA = central apnoea index; hGH = human growth hormone; HI = hypopnea index; IGF-1 = insulin-like growth factor 1; IQR = interquartile range; LBM = lean body mass; NS = not significant; ODI = oxygen desaturation index; OSA = obstructive sleep apnoea index; REE = resting energy expenditure; SD = standard deviation; SDS = standard deviation score; SF = skin fold measurements; SRBD = sleep-related breathing disorders.

Appendix 5: Additional References of Potential Interest

Retrospective chart review on age-related trends in GH stimulation test results

Cohen M, Harrington J, Narang I, Hamilton J. Growth hormone secretion decreases with age in paediatric Prader-Willi Syndrome. Clin Endocrinol (Oxf). 2015 Aug;83(2):212-5.
[PubMed: PM25495188](#)