REVIEW OF
WEDNESDAY & THURSDAY'S
MEDICAL & SCIENTIFIC MEETING

Friday June 23, 2023
David Agarwal, MD, FSIR

United in Hope FOR PWS

PWSA | USA 2023
NATIONAL CONVENTION

June 21 – 24, 2023 • Orlando, FL

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Moderators

James Loker MD, Bronson Healthcare, Kalamazoo, MI, USA
Ann Manzardo PhD, Univ Kansas Med Ctr, Kansas City, KS, USA

- Thank you to Jim, Ann, Clinical and Scientific Advisory Board, Paige Rivard, Kristi Rickenbach, Angela Frazier, and everyone it takes to run an awesome conference like this!
- The 2023 Medical & Scientific Conference was all day Wednesday and Thursday morning, with highlights being 1 Keynote speaker and 3 other Expert presentations.
- Also 1 roundtable discussion, 9 abstracts, and 8 scientific posters.

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Overview of the Newly Formed Clinical/Scientific Advisory Board (CSAB)

Ann Scheimann MD MBA, Johns Hopkins School of Medicine, Baltimore MD

- Separate Scientific and Clinical Advisory Boards
  - 1979 Scientific Conference
  - 1983 Scientific Advisory Board
  - 2000 Clinical Advisory Board
  - 2002 Crisis Interventional Program
- The combined Board
  - Provides expert clinical and scientific guidance to PWSA|USA
  - Ensures policies & grants meet highest standards of scientific accuracy

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Behaviour & Mental Health in PWS: Understanding Mechanisms and the Potential for New Treatments

Anthony Holland MD, University of Cambridge, Cambridge UK. President of IPWSO

2023 KEYNOTE SPEAKER

- The neuropsychiatric characteristics of PWS are well described. We need better understudying of the underlying biological mechanisms that give rise to hyperphagia and these behaviors.
- Clinical trials, positive or negative, help us understand biological pathways that may lead to helpful medications or eliminate pathways less likely to be successful. Challenges include:
  - Uncertainty of basic underlying pathophysiology.
  - Practical financial and governance challenges.
  - Living circumstances that include food insecurity limit value of observational questionnaires.
- Our ongoing goal is to understand the cause-and-effect relationship between gene expression or non-expression, brain structure and function, and these outward traits.
- Also, echoing the IPWSO Mental Health Initiative, to capture the pattern of atypical brain development that shows the dimensions of mental ill-health associated with PWS.

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Behaviour & Mental Health in PWS: Understanding Mechanisms and the Potential for New Treatments

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2023 KEYNOTE SPEAKER

- Common theme of today's presentations: understand behavioral & mental health impairments based on biological/genetic pathways, from description to understanding to intervention.
- How do specific research findings change our understanding of the neural mechanisms that underpin the neuropsychiatric phenotype of PWS?
- Examples of exciting papers that changed how we think about PWS (Dr. Holland described these as transformative moments):
- Key observation: decreased but not absent satiety response to food (with high levels of CCK in PWS group, so people with PWS can feel full but only after 3x more calories and with more rapid return of hunger after eating.
  - *TAKEAWAY: is CCK inactivated or is there a receptor or post-receptor deficit?*

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- Key observation: hunger and satiety are conscious experiences so must be linked to cerebral cortex, neuroimaging comparing a group with changed hunger ratings vs group with no change showed changes of cortical activation but also significantly smaller hypothalamus. So, is this structural abnormality a consequence of development or genetics?
  - *TAKEAWAY: either way, can we potentially target impaired function or enhance hypothalamic development after birth?*
- Key observation: emotional outbursts have a recognizable pattern, neurofunctional difference in task switching, vagus nerve stimulation is effective in suppressing outbursts, life changing for parents, suggests the main driver is the nervous system.
  - *TAKEAWAY: does changing parasympathetic tone provide time to allow sufficient cognitive processing to resolve issues, better adaptation/coping?*

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Behaviour & Mental Health in PWS: Understanding Mechanisms and the Potential for New Treatments

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2023 KEYNOTE SPEAKER

- Key observation: risk of affective (mood) disorders is shared across the 15q11.2-q13 PWS genotype but psychotic illness occurs more in people with UPD than deletion, now recognition provides the opportunity for effective treatment.
  - *TAKEAWAY: develop a predictive coding model to screen and treat, first see how groups differ, then provide options.*
- SUMMARY: PWS is a disorder of atypical brain development specifically hypothalamic dysfunction and impaired homeostatic regulation including feelings, this impacts secondary body systems, eg brain's impaired ability to respond to changing physical and psychological demands leads to impaired mental health.
- Understanding behavioral & mental health impairments based on biological/genetic pathways, from description to understanding to intervention.

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Abnormal Response Monitoring in PWS: A Novel Phenomenological Explanatory Model

Deepan Singh MD, Maimonides Medical Center, Brooklyn NY

2023 SPEAKER

- Response monitoring: the capacity to flexibly adapt to dynamic environments,
  - Uncertainty is processed using planning, judgment, effort appraisal, emotion, drive, arousal, leading to a behavioral decision, which can be adaptive or maladaptive. In general, we take the easier way out, that becomes the outcome pathway.
  - One meltdown (or shut-down) can severely impact surrounding people (and impact questionnaires & validity of assessment tools). A behavior therapist can break the cycle of maladaptive behavior.
  - Psychosis is common, take it seriously, it's not schizophrenia, watch for sudden changes in behavior, eg not sleeping, not seeking food. Get help, this is treatable, expect a rapid response to treatment.

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Abnormal Response Monitoring in PWS: A Novel Phenomenological Explanatory Model

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- Is guanfacine an alternate pathway?
  - Vagus nerve stimulates the parasympathetic system from the outside.
  - Guanfacine is a selective alpha-1 adrenoceptor agonist that acts centrally on the brain.
  - Being studied to treat irritability, aggression, self-injury/picking with promising interim analysis.
- Last topic hyperphagia
  - Not the same as hunger, partly faulty satiety.
  - Echo'd Dr. Holland, using a dysfunctional waterfall model, with genetic and neurobiological causes of behavioral abnormalities.
  - Critical region 15q11-13, central role of hypothalamus and connections to other brain structures.

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Growing with Sexual Development and Stress

Moris Angulo MD, Good Samaritan University Hospital, West Islip NY

2023 SPEAKER

- PWS started with hypothalamic-pituitary dysfunction, hyperphagia, but also sleep disordered breathing, temperature instability, high pain threshold.
  - Value of ratio of head to chest circumference, 4-5x normal in PWS, if hypotonia then PWS.
  - 30% of unexplained neonatal hypotonia may be PWS, later short stature, impacted by early GH deficiency and mean parental height.

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Growing with Sexual Development and Stress

Moris Angulo MD, Good Samaritan University Hospital, West Islip NY

2023 SPEAKER

- GH affects LH/FSH, TSH, ACTH/cortisol, prolactin - each up/down regulates the other.
  - Using GH, most increase in growth velocity is in 1st 2 yrs, can give sex hormones to optimize bone mineral density, reviewed value of IGF-1 and IGF-BP3.
  - Stop GH if side effects including edema, insulin resistance, T2DM, no longer efficacious, DM, primary or secondary malignancy, no further expectation of advancing bone age.
  - Check for premature adrenarche, polycystic ovarian syndrome, central adrenal insufficiency (CAI, not different from general population) -> lab testing, include sex hormone binding protein.

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Outcome Measures for Prader Willi Syndrome: How Far Have We Come and Where We Need to Go

Jessica Duis MD, University of Colorado, Denver CO

2023 SPEAKER

- 123 studies in clinicaltrials.gov, 90 interventional, 8 with results.
- Genotropin, indication for use in peds PSWA, fat mass, lean body mass.
  - Other 8 used hyperphagia questionnaire or body measurements.
- PATTERN: Body composition, hyperphagia questionnaire.
- Why don't we have more drugs approved? Because we don't meet primary outcomes, maybe "suggested benefit" – so we need better study designs.
- Lesson 1: objectively assess something important to families (and relevant to the mechanism of the drug) - must accurately measure the most important symptoms to caretakes and clinicians.
  - Social listening – neurological sleep disorders (hypersomnia, narcolepsy, cactaplexy) were missed in the original descriptions of PWS.

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Outcome Measures for Prader Willi Syndrome: How Far Have We Come and Where We Need to Go

Jessica Duis MD, University of Colorado, Denver CO

2023 SPEAKER

- Lesson 2: Quantitate with correlative biomarker.
- Lesson 3: Measures changing aspect of disease over time.
- Lesson 4: Measured in natural environment.
- Lesson 5: Correlated to other features of disease.
- Lesson 5: Clinically meaningful change can be assessed during clinical period.

- 9 item Hyperphagia Questionnaire for Clinical Trials (HQ-CT).
- Our studies need to:
  - ensure we capture the right outcome from the targeted effect of the drug.
  - consider a more subjective (caregiver interview) coupled with an objective measure (weight).
  - Have tighter qualifying criteria (eg BMI > 95% for age).

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Roundtable - PWS Clinical Trial Endpoints

Moderated by Anthony Holland MD, University of Cambridge, Cambridge UK

Theresa Strong MD, Director of Research Programs, Foundation for Prader-Willi Research
Anxiousness in PWS, The *PWS Anxiousness* and Distress Behaviors Questionnaire (PADQ)
- How can we measure anxiety in a clinical trials?
- PADQ development: observable behaviors, FDA guidelines, COA best practices, working groups, iterative qualitive interviews with PWS caregivers.

Janice Forster MD, Developmental Neuropsychiatrist, Pittsburgh Partnership
PWS Personality Questionnaire (PWSPQ): Tools for Assessing Phenotypic Endpoints in PWS
- 6 domains, food drive, non-food drive, stress sensitivity and mood symptoms, skin picking, impulsive and disruptive behavior, cognitive rigidity.
- Could use non-food drive traits such as cognitive rigidity as outcome measures for trials.

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Roundtable - PWS Clinical Trial Endpoints

Moderated by Anthony Holland MD, University of Cambridge, Cambridge UK

Maria Picone, Founder/CEO, TREND Community
Adaption and Development of Goal Attainment Scaling for PWS
- Subjective measures, FDA recommends personalized endpoints, "most bothersome symptom."
- Formal framework to assess the lived experience of the individual and their family.
- AI to assess terms being used on social media discussions about PWS.
- Will interview caregiver and person affect by PWS.

Jessica Duis MD, Pediatrics and Genetics, University of Colorado
Clinical Global Impressions (CGI) Scale
- NIMH sponsored trials, a clinician's view of how the patient is doing, start with a severity scale. (CGI-S), follow an improvement scale (CGI-I) over time, no caregiver data, still subjective.

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PATH for PWS 2023 Update: A Non-Interventional, Observational, Natural History Study of Serious Medical Events in PWS

Lisa Matesevac, Study Coordinator, Foundation for Prader-Willi Research

- Sub-study of parent-reported Global PWS Registry.
- Enrolled 700 over 9 mo from 2018-2019, 84% retention, 60% completed 4yr end survey.
  - 48% with 1 adverse event, of these 84% had multiple events.
    - 24% - mental health, 50% were extreme aggression.
    - 17% - GI, 33% were constipation.
    - 17% - orthopedic, 49% are scoliosis.
    - infections, COVID # = 24, was 40% of reported infections, very few hospitalizations.
    - DVT # = 7, 1 with 2 events.
- Hyperphagia Questionnaire for Clinical Trials (HQ-CT), wide range of scores.
  - Higher scores correlated with BMI, food insecurity.
  - Low scores with acclimation to routine, caregiver control of access to food.
- Last data fall 2023, look at subgroups, meds and changes with age, behavior, support trials.

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The Lived Experience of Parents of Children with PWS

Terrilynn Fox Quillen RN MSN PhD, Saint Louis University, St. Louis MO

- To identify parents' daily feeding habits and practices that promote food security inside and outside the home.
- Brief excerpt of her doctoral dissertation, was awarded with distinction by the Trudy Busch Valentine School of Nursing in May 2022.
- Creating a secure food environment, "unity in diversity" in food security approaches to feeding the entire family.
- 7 rights of food security in the family, similar to appropriate use of medications:

to the right person	in the right quantity	for the right purpose
by the right person	in the right place	
with the right foods	at the right time	

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Cognitive Rigidity – Phenotype Fidelity in PWS

Janice Forster MD, Pittsburgh Partnership, Pittsburg PA

- Cognitive and behavioral characteristics of cognitive rigidity.
- Emergence of phenotypic traits reflects underlying brain development.
- 6 domains of the PWS phenotype using the PWS Personality Questionnaire,
  - Food drive
  - Non-food drive
  - Sensory hunger and skin picking
  - Stress sensitivity,
  - Impulsive and disruptive behavior
  - Cognitive rigidity
- Cognitive rigidity has greatest fidelity in defining the behavioral phenotype of PWS
- Indicator of psychological inflexibility (difficulty changing cognitive sets) that reflects an inability to see alternative points of view or solutions to a problem.

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Current Research in Behavioral Analysis and PWS

Kasey Bedard PhD BCBA-D, Delta Behavior Services, Gainesville FL

- Overview of variety of current studies evaluating analytic interventions for PWS related behaviors and skill deficits.
- Current survey research:
  - Toilet training and related challenges.
  - Self-care skills.
  - Play skills.
  - Repetitive verbal behavior.
  - Also: residential programming.
- Goal: understand behavior, management strategies, use interventions including applied behavioral analysis to improve quality of life.

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Evaluating Electronic Health Record Data in Individuals with a Defined Computable Phenotype for PWS

Olivia Veatch PhD, University of Kansas Medical Center, Kansas City KS

- Genetic factors relative to comorbidities.
  - eg sleep disorders specifically sleep disordered breathing.
- Manual review/extraction after initial EHR screen.
  - Lots of false positives.
  - Even misdiagnoses.
- The most prevalent non-PWS clinical codes during 1st year after coded as PWS:
  - Children - obstructive sleep apnea (27%).
  - Adults - no prevalent comorbid diagnoses identified (n≤5 per non-PWS code).

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Neuropsychiatric Manifestations of Post Infectious Syndromes in a Case Series of Patients with PWS

Linda Gourash MD, Pittsburgh Partnership, Pittsburgh PA (presented by Dr. Forster)

- Pediatric Autoimmune Neuropsychiatric Syndrome (PANS).
  - No reports in PWS, but may be overlooked due to phenotype associated mental illness.
  - Can affect neurons in the basal ganglia, so presentation includes intense behavior changes, tics and/or OCD behavior.
  - PANS encephalitis may mimic clinic psychosis in PWS.
  - Presented 6 non-PWS cases.
- Inflammation disrupts pathways: need to eliminate pathogen, suppress inflammation, allow healing, prevent recurrence.
- 3 clusters: emotional lability, acute onset tics/OCD, food restriction.
- Extreme pain and suffering.
- Symptoms of PABS overlap with PWS phenotyope, motor symptoms may be best discriminator.

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Infants with PWS: A Critical Period for Diagnosis, Evaluation, Management, & Treatment based on French Experience and European Studies

Maithe Tauber Pr, Toulouse University Hospital, Touluse FR

- Optimizing care of infants with PWS and their parents.
- 3 groups: 2005-2009, 2010-2014, 2015-2021.
- Mean age of diagnosis has decreased from 32 to 18 days.
- Changes may reflect earlier diagnosis, changes in clinical practice, improved knowledge, and setting standards to care, eg GH.
- Applied to oxytocin research since 2017, involved feeding and social skills, oxytocin first, then response, then GH.
- Need guidelines, appropriate standard of care to standardize Rx.
- Research keeps patients in the system, allows longitudinal care.

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Quality Improvement Project to Improve Puberty and Reproductive Health Counseling of Patients with PWS

Hiba Salhah MD, The Ohio State University, Columbus OH

- Hypogonadism affects more than fertility - bone health, body composition, metabolic homeostasis.
- Improve rate of comprehensive puberty and reproductive health counseling in M&F with PWS (8-21yo) seen in a multidisciplinary PWS clinic from baseline of 5% toward goal 80%.
- IPSWO educational handout given PWS patients and caregivers to review on sexual development.
- Puberty and reproductive health counseling which included discussion of typical pubertal development and risk for hypogonadism, possible need for HRT, and fertility potential.
- Became of of standard processes within best practices.

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Experiences & Support Needs of Unaffected Siblings & Parents of Individuals with PWS, A Qualitative Study

Meghana Wadnerkar Kamble PhD, University of East Anglia, Norfolk UK

- Healthy siblings of people with a chronic neurodevelopmental condition can experience associated stresses that impact on their personal and social development.
- Siblings and parents have a different view on the influence that a child with learning difficulties has on their sibling .
- GROUPS: sibs 11-13 years, sibs 14-17 years, sibs 17 years+, and parents
- Stage I = listen, Stage II = understand support needs, Stage III - provide support
- Preliminary findings indicate themes around isolation, stressors around food and lifestyle management, and the role of sibling as caregiver.
- Emphasized family communication, peer-peer support.

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