Hypothalamic obesity

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Center for Mitochondrial and Epigenomic Medicine
Children's Hospital of Philadelphia

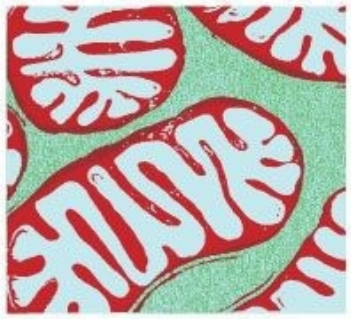
Penn Institute for Diabetes, Obesity and Metabolism

CHOP Neuroendocrinology Family Symposium
March 16, 2019

Children's Hospital of Philadelphia℠

Perelman School of Medicine
University of Pennsylvania

Institute for Diabetes, Obesity, and Metabolism



Disclosures

- Rhythm Pharmaceuticals, Hypothalamic Obesity Advisory Board
- Rhythm Pharmaceuticals, Genetic Obesity Steering Committee
- Site PI, Levo Pharmaceuticals (Prader-Willi Syndrome)
- Reata Pharmaceuticals, Advisory Board

Off-label use of medications: some medications used for weight loss are approved for other indications, and/or some may not be approved for use in children.

Gratitude

- Children's Hospital of Philadelphia Neuroendocrine Center Faculty & Family Advisory Committee
- Chiang family
- Meeting organizers & volunteers
- Participants, patients, & families
- Attendees!

Raymond A. Wood foundation

Pediatric
Pituitary
Brain Tumor
Workshop

Saturday
March 16, 2019

Goals

- Offer ideas to review with the usual care team
- Gather priorities for care, research, and education for the CHOP Neuroendocrine Center (literally!)

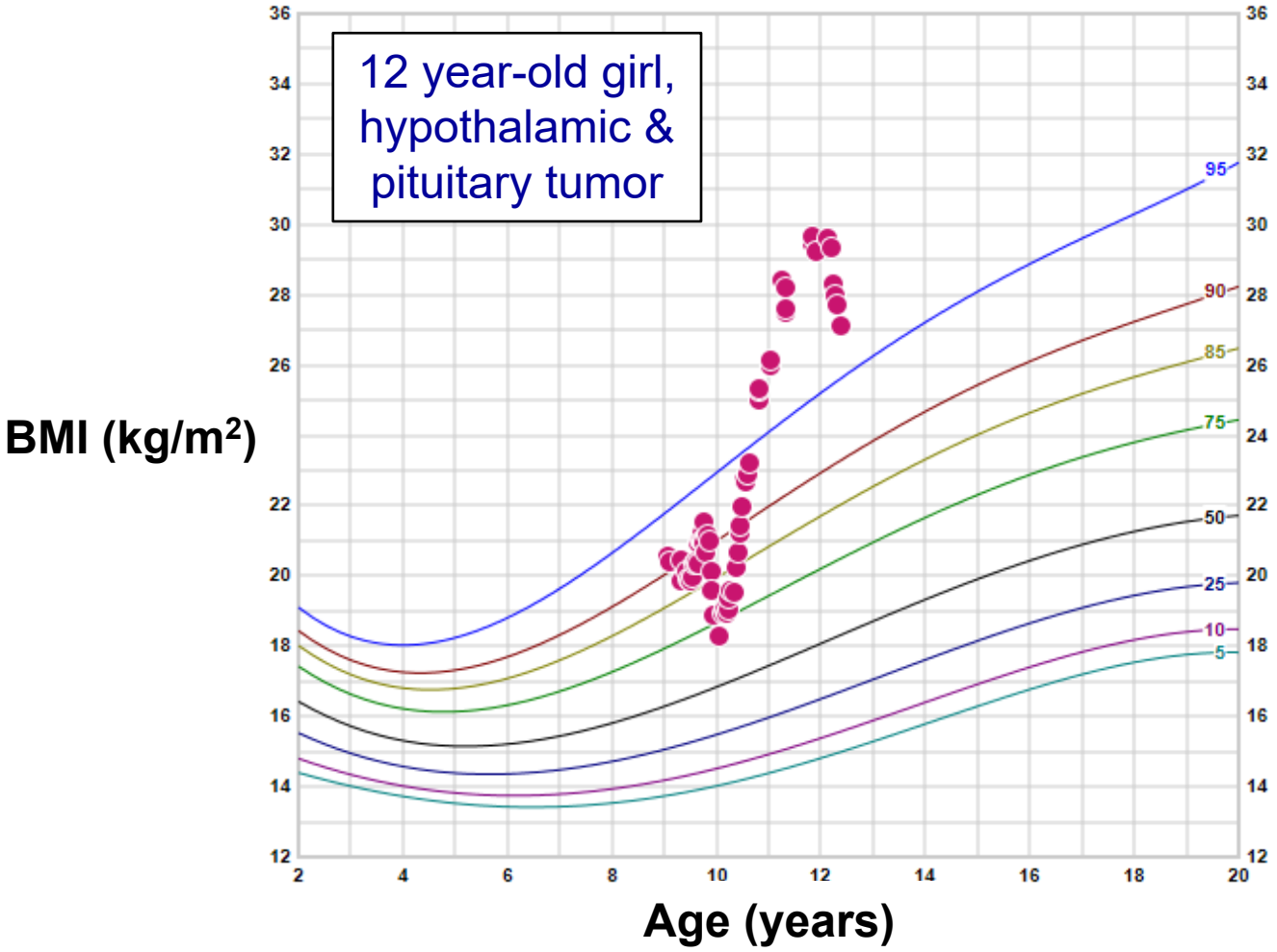
Caveats

- Much remains to be learned
- No “one size fits all” solution

Notes

- “PMID” means PubMed ID (www.pubmed.gov)
- U.S. clinical trials are at: www.clinicaltrials.gov

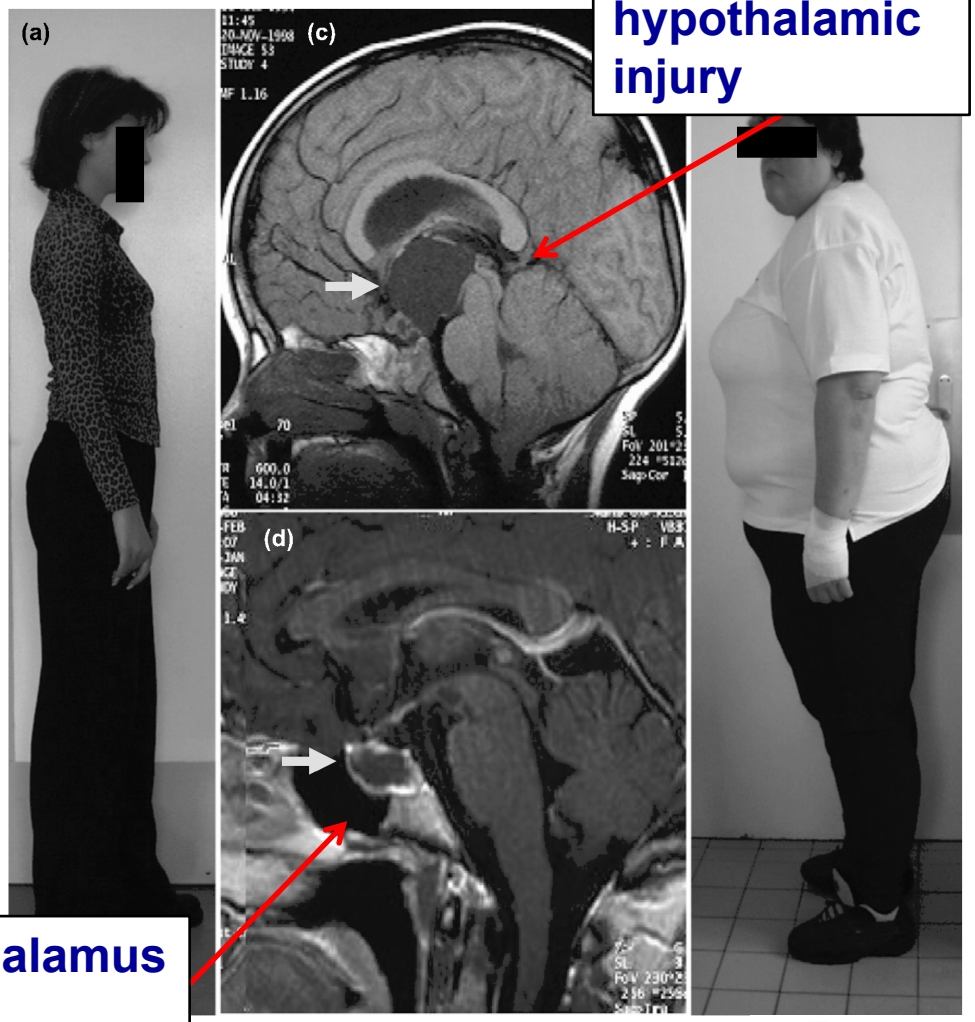
Hypothalamic obesity is a unique clinical challenge.



What can we offer this patient that will work?

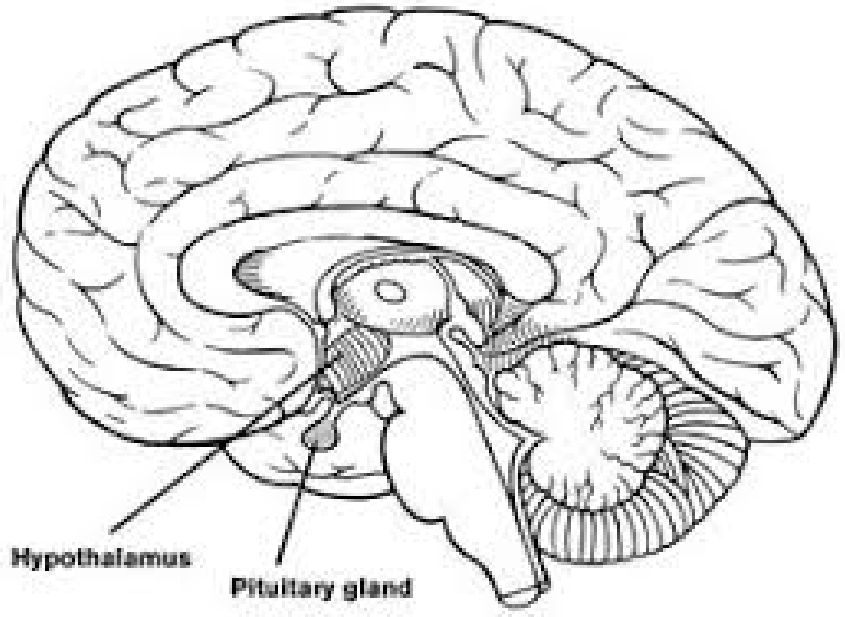
Why does obesity occur with some hypothalamic/pituitary tumors?

- **Anatomy** determines risk.
- *Tumor types include:* craniopharyngioma, astrocytoma, medulloblastoma.
- *Other risks factors:* younger age, endocrinopathy, BMI at presentation, maternal BMI.



Muller et al., Klin Padiatr 2003 (PMID: 14677094)
Roth et al., Obesity 2015 (PMID: 25884561)
Haliloglu et al., Ped Obes 2016 (PMID: 26463004)

Isn't all obesity hypothalamic?



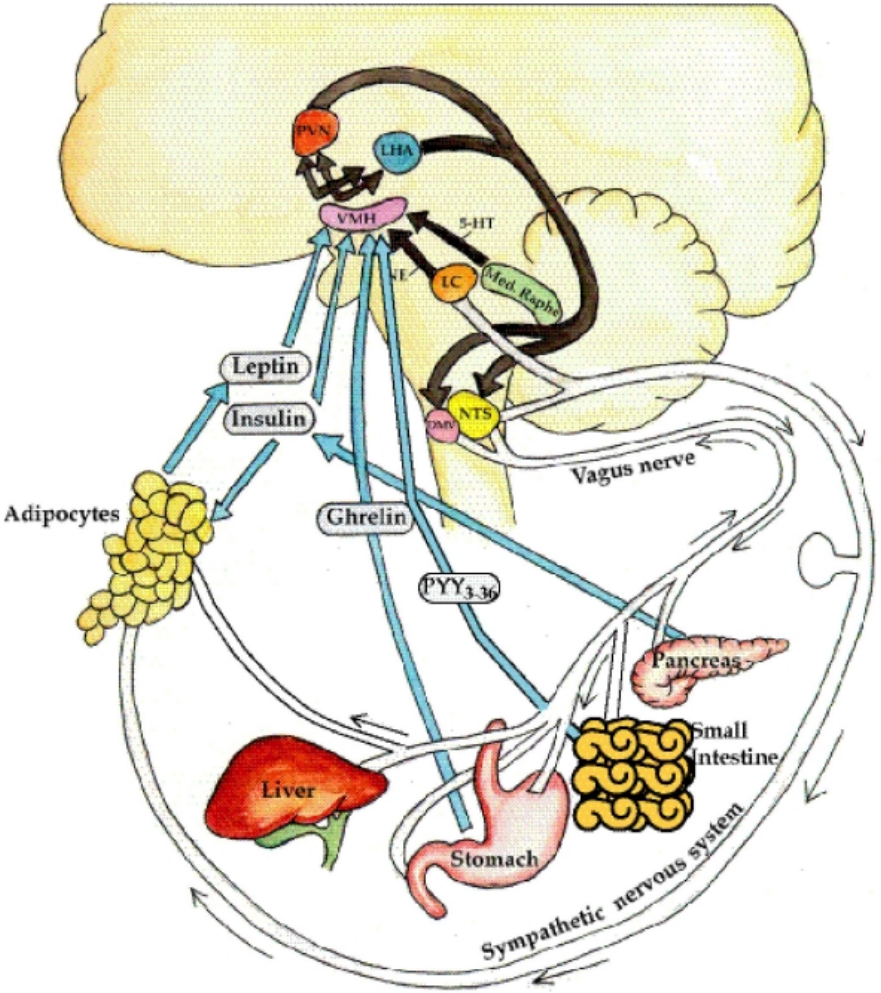
Proposed definition (Lustig, JCEM 2003):

- Brain tumor affecting the hypothalamus
- [At least one endocrinopathy] = evidence of damage
- Excess rate of weight gain

Lustig et al., JCEM 2003 (PMID: 12788859)

The hypothalamus perceives energy availability, and then affects intake (+, eating and storage) and output (-, satiety and expenditure)

+



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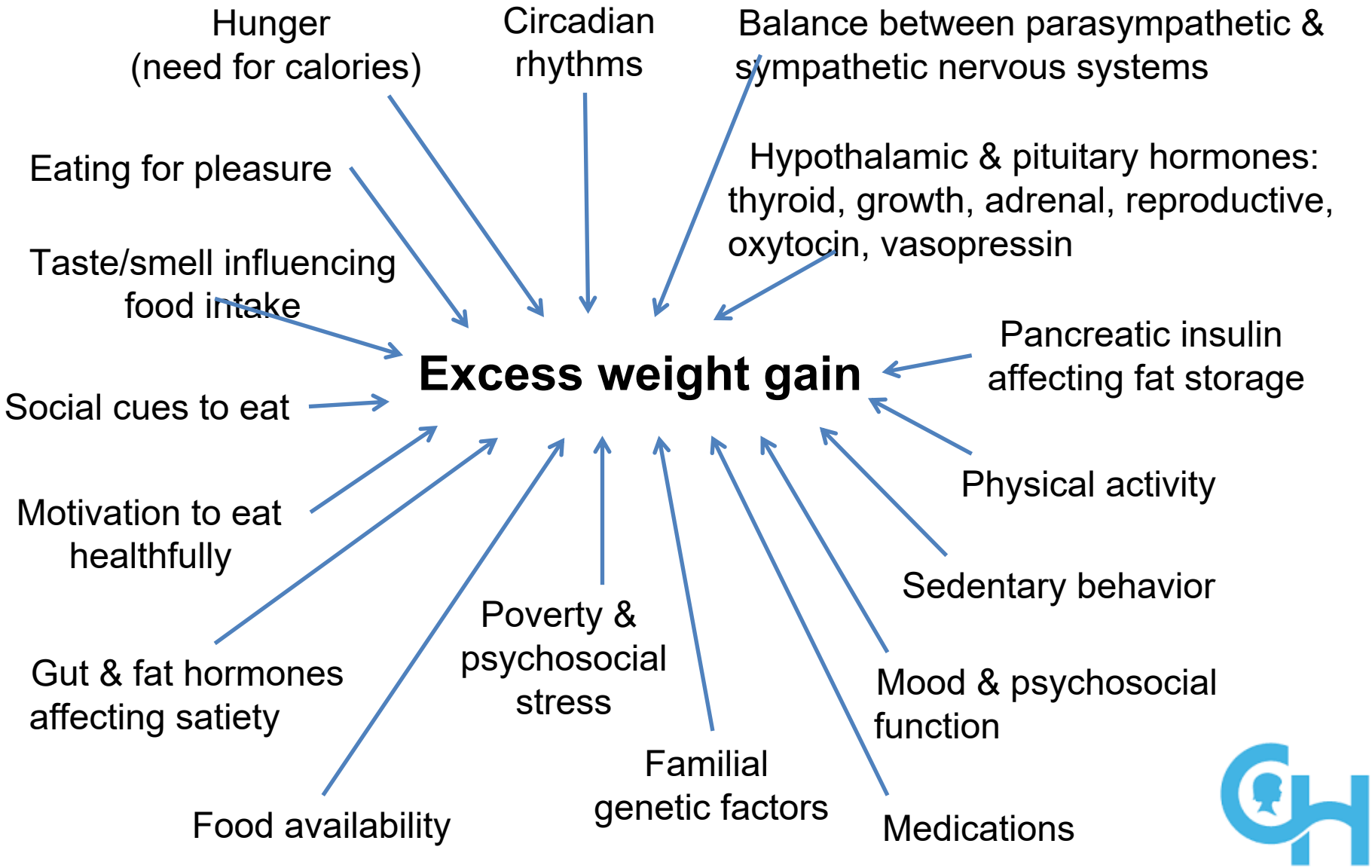
Lustig et al., JCEM, 2003 (PMID: 12574189); Lustig, Obesity, 2011 (PMID: 22654817)

The brain does not perceive all of the energy around (stored as fat), and so goes into “starvation mode”.

“Water, water, every where,
Nor any drop to drink”

Samuel Taylor Coleridge
Rime of the Ancient Mariner

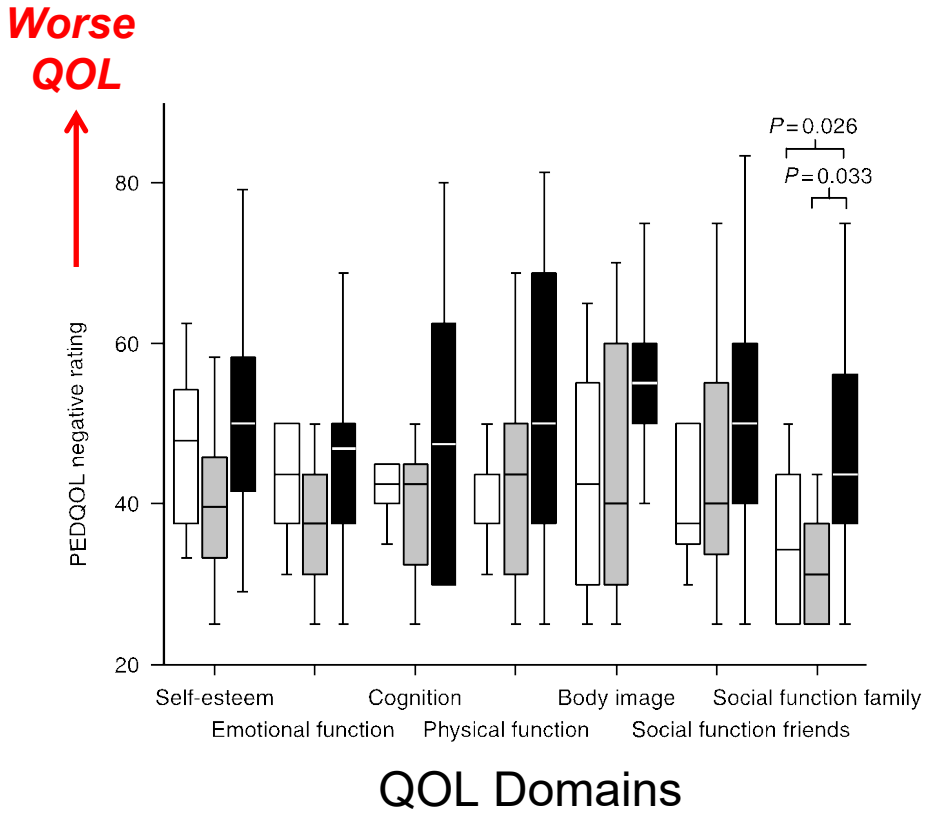
Individual variation in factors contributing to hypothalamic obesity.



Decreased energy expenditure is the most consistent feature.

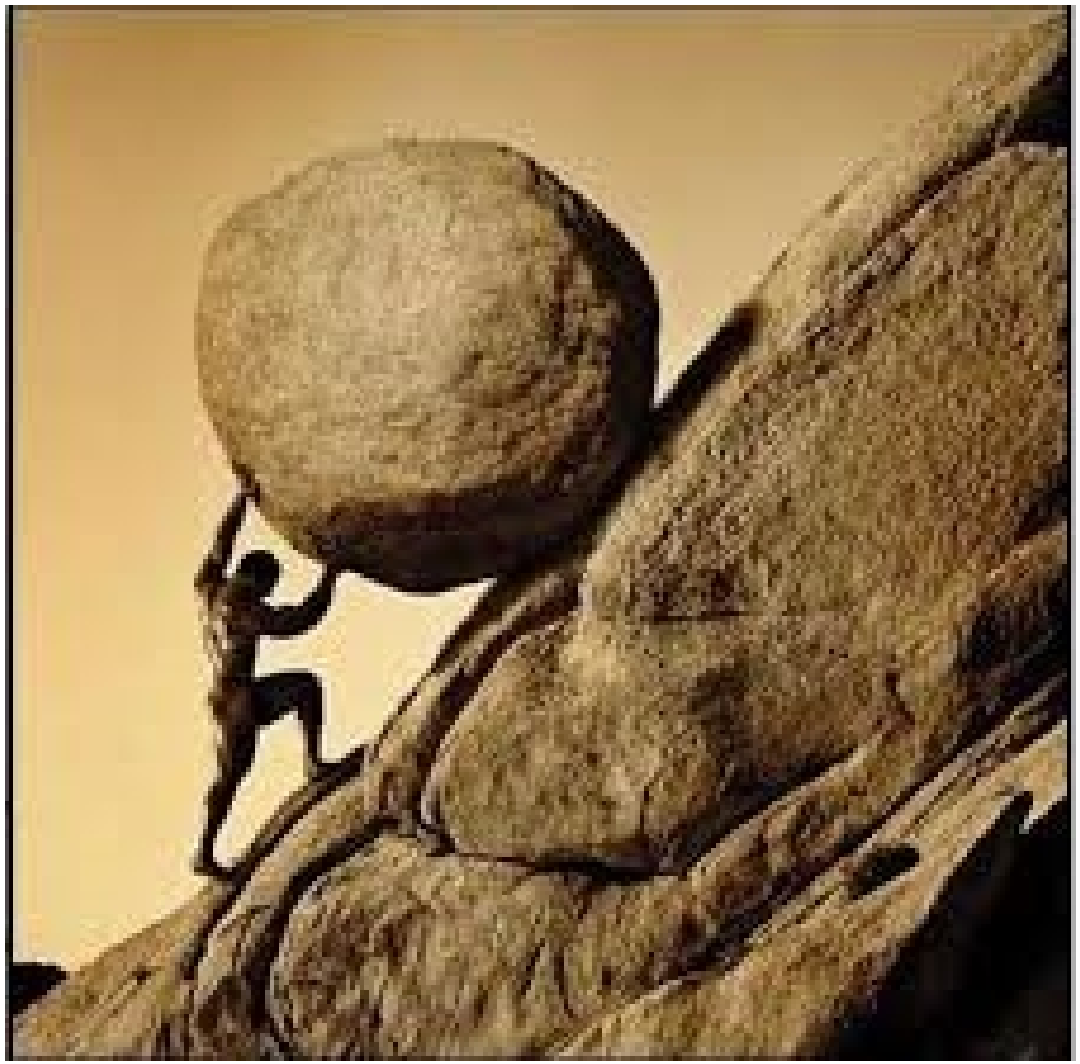
Why?

- Increased parasympathetic and decreased sympathetic activity.
- High insulin levels
- Disordered circadian rhythms
- Decreased activity
- Decreased socialization



Harz et al., JCEM 2003 (PMID: 14602754); Muller, Eur J Endo 2011 (PMID: 21490122)
Hoffman et al., JPEM (PMID: 25503864); Bomer et al., JPEM (PMID: 28097839)

What should we do?



Research

Thanks to:

FARA Friedreich's Ataxia Research Alliance

Important background:

- *Options:* learn (& propose!) www.clinicaltrials.gov
- *Equipoise:* stay neutral, balanced, and detached from the outcome (even if a lot is invested)
- *Oversight:* funding agency, FDA, IRB, DSMB, investigators & participants
- *Non-FDA approved medications in research:* require IND, including certificate of analysis, demonstration of stability, microbe & pyrogen testing

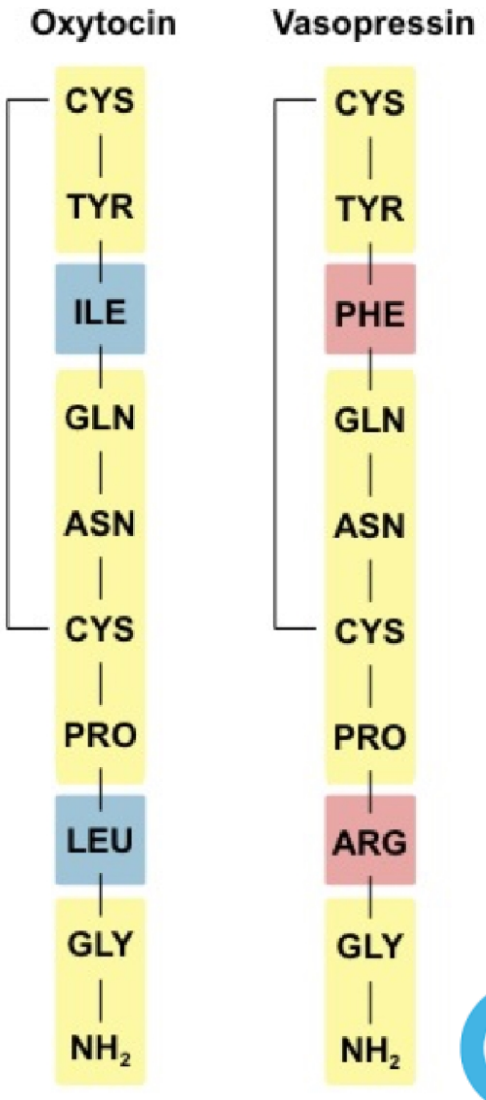
Research

Clinical trials in brain tumor related obesity ongoing include:

- NCT02664441 (PI, Christian Roth, University of Washington): “Energy balance & weight loss in craniopharyngioma-related or other hypothalamic tumors in hypothalamic obesity (ECHO)”, 10-25y, exenatide (GLP1-R agonist)
- NCT02849743 (PI, Shana McCormack, CHOP): “Intranasal oxytocin for hypothalamic obesity”, 10-35y, intranasal oxytocin
- Immune modulation for new/recurrent CP, Todd Hankinson (Colorado), Eugene Hwang (Children’s National Medical Center)

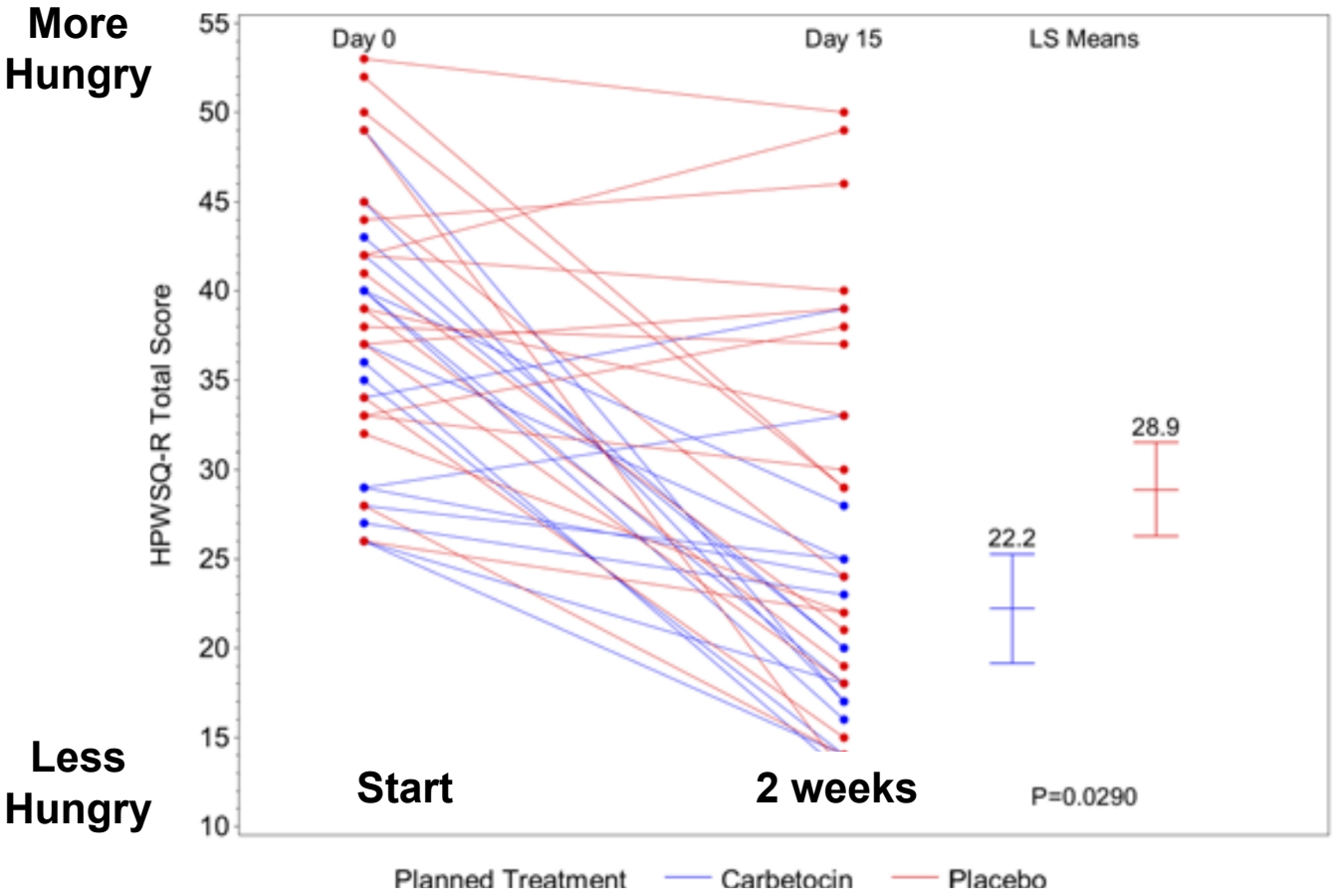
Intranasal Oxytocin (OXT): Rationale for use in Hypothalamic Obesity (HypOb)

- 9-AA peptide made in hypothalamic paraventricular and supraoptic nuclei
- Animals: OXT promotes fat loss, spares lean mass.
- Obese adults: OXT may decrease energy intake and promote weight loss.
- Abnormal OXT in HypOb is plausible, and replacement may be helpful.
- Well-tolerated, but risk for hyponatremia exists.



PMID: 25865294; PMID: 27585663; PMID: 29480934; PMID: 29220529

Carbetocin (OXT analog) decreases parent-reported hyperphagia in Prader-Willi Syndrome



Dykens et al., JCI Insight 2018 (PMID: 29925684)

What are clinicians offering?

Natural history (U.S., n=87, 86% brain tumors):

Original Article
CLINICAL TRIALS AND INVESTIGATIONS

Obesity

Hypothalamic Obesity: 4 Years of the International Registry of Hypothalamic Obesity Disorders

Susan R. Rose [1], Vincent E. Horne [1], Nathan Bingham[2], Todd Jenkins[3], Jennifer Black[3], and Thomas Inge[4]

Rose et al., Obesity 2018 (PMID: 30296362)

What are clinicians offering?

TABLE 4 Treatment options ($n = 87$)

	Total	Percentage
Dietitian supervised	37	52.1
Physician supervised	29	40.8
Nutritional counseling	71	81.6
Pharmacological therapy	51	58.6
Metformin	27	52.9
Dextroamphetamine	12	23.5
Methylphenidate	8	15.7
Orlistat	7	13.7
Ephedrine	5	9.8
Caffeine	3	5.9
Sibutramine	2	3.9
Octreotide	1	2.0
Venlafaxine	1	2.0
Sleeve gastrectomy	4	57.1
Roux-en-Y gastric bypass	2	28.6
Laparoscopic band	1	14.3
Bariatric surgery	7	8.0
Vagal nerve stimulator	1	1.1
No treatment reported	9	10.3

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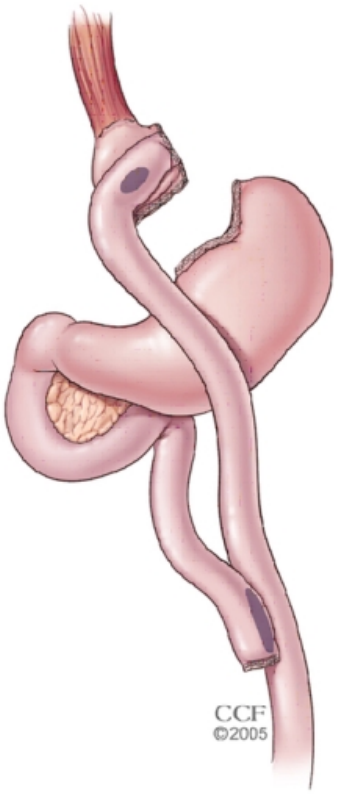
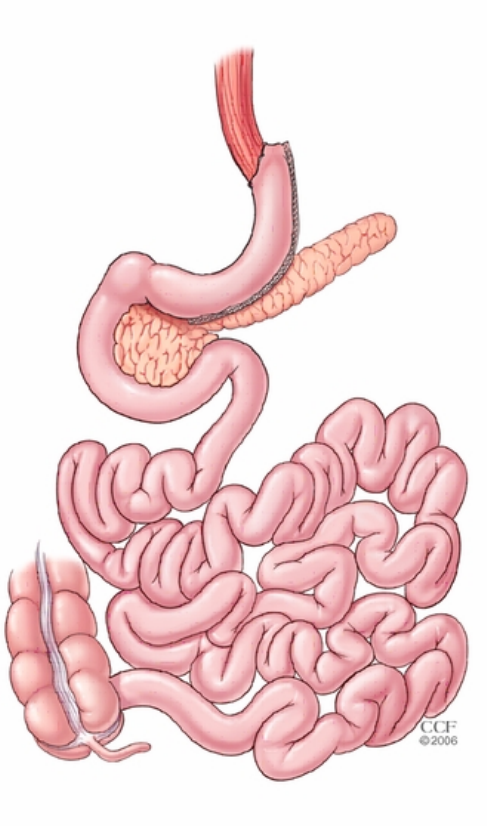
Metabolic Surgery



Roux-en-Y gastric bypass



Sleeve gastrectomy

Likely most efficacious:

- At 2.6 years, median decrease in BMI 8.2 kg/m^2 (depends on procedure)
- Mean weight loss after 6 months 20.9 kg (n=21), gastric bypass most effective (meta-analysis)
- Many likely meet ASMBS criteria for procedure (BMI 120% of 95%ile with comorbidities or 140% of 95%ile without)

Rose et al, Obesity, 2018 (PMID: 30296362)
Bretault et al., JCEM, 2013 (PMID: 23533238)
ASMBS criteria, 2018 (PMID: 30077361)

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Pharmacotherapy (key points)

Modest benefits need to be balanced against risks:

Option	Benefits	Risks
Stimulants	pediatric experience may help ADHD & fatigue	increases in heart rate and blood pressure
Metformin	pediatric experience may help delay diabetes	GI upset
GLP1-R agonists (e.g., liragultide, exenatide)	research & some clinical pediatric experience, including craniopharyngioma	nausea fatigue
diazoxide (+/- Metformin)	targets high insulin	fluid retention high blood sugars
octreotide	targets high insulin	gallstones high blood sugars
orlistat	pediatric experience	fat in stool
topirimate	pediatric experience helps with migraine	acidosis cognitive effects at higher doses

More adult experience: Phentermine/Topirimate, Lorcaserin, Bupropion/Naltrexone, Pramlintide, Zonisamide

Stimulants (PMID: 12197795); Metformin/fenofibrate (PMID: 25536662); Exenatide (PMID: 27133664); Octreotide (PMID: 12718557); Diazoxide/Metformin (PMID: 21603206); Systematic review in pediatric HypOb (PMID: 28544764)

Pituitary Replacement

Thyroid:

- Thyroid hormone levels in the upper part of the normal range with levothyroxine (T4).
- One study of liothyronine (T3) monotherapy in CP found no change in brown fat activity, sympathetic activity, resting energy expenditure, or BMI.
- Although evidence is limited, per ATA consideration of 3-6 month trial of T4 + T3 (with small amount of T3 several times per day) is reasonable.

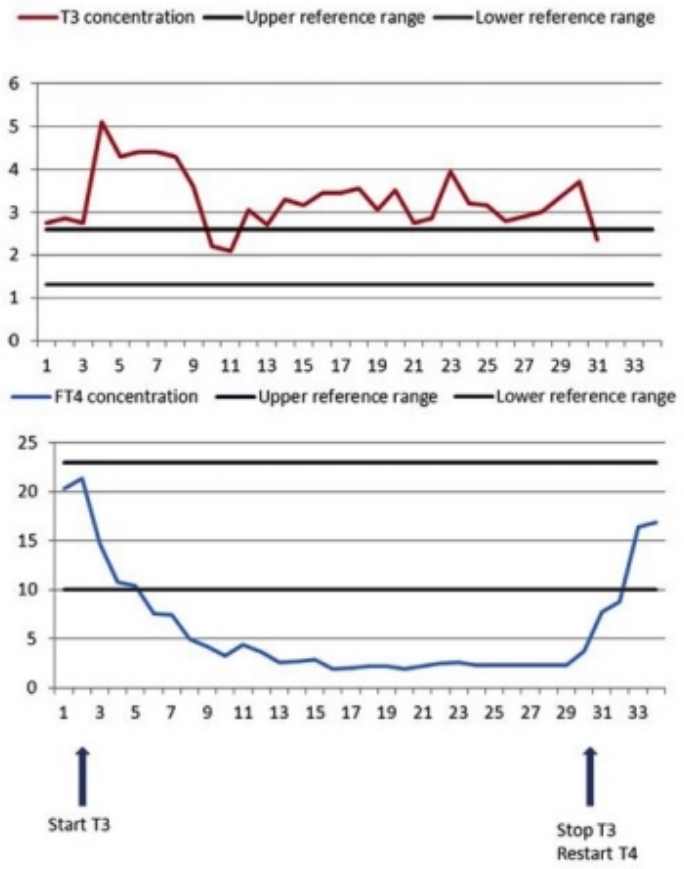


Figure 2 Plasma concentrations of plasma T3 (nmol/L) (A) and FT4 (pmol/L) (B) right before, during, and after changing T4 treatment to T3 monotherapy.

Van Santen et al., JPEM 2015 (PMID: 25514327)

Pituitary Replacement

Growth hormone:

- GH as soon as is feasible (early initiation may have benefits for weight and neuropsychological outcomes). Be thoughtful about weight-based dosing.
- “Growth without GH” can occur.
- GH has lipolytic and anabolic effects, and lower doses may be continued into adulthood.

Boekhoff, …, Muller. Eur J Endo 2018 (PMID: 30139824)

Pituitary Replacement

Glucocorticoid:

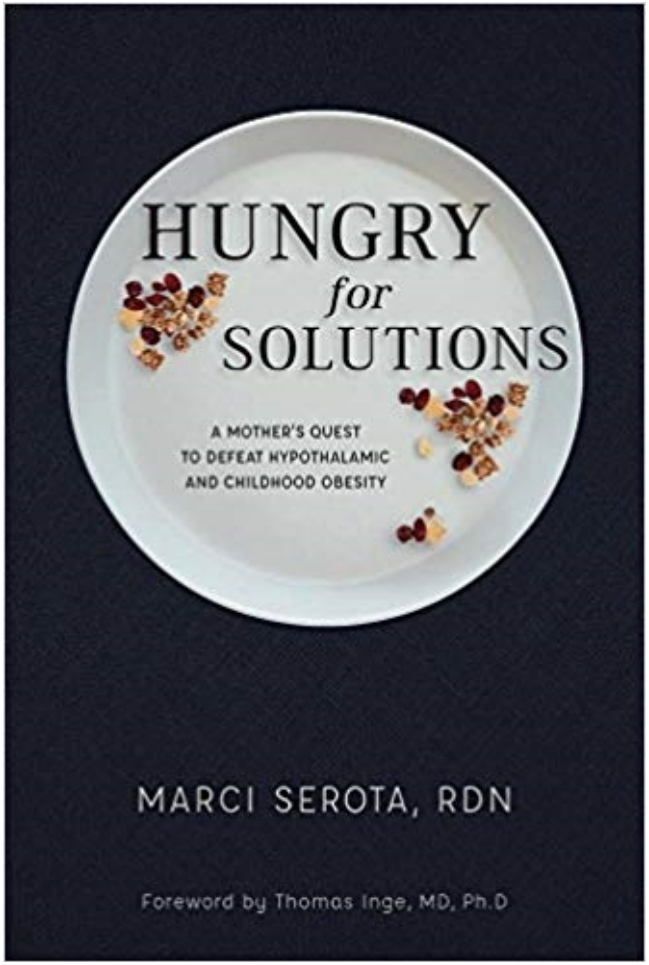
- Use lowest effective glucocorticoid replacement, be thoughtful about timing and size-based dosing.
- Lower doses may be needed, related to potential differences in cortisol metabolism (? increased 11-β-HSD1 activity).
- Dose based on symptoms, endogenous function

Hochberg et al., Horm Metab Res 2004 (PMID: 15241725)

Diet & Exercise

These are still <u>really</u> important!

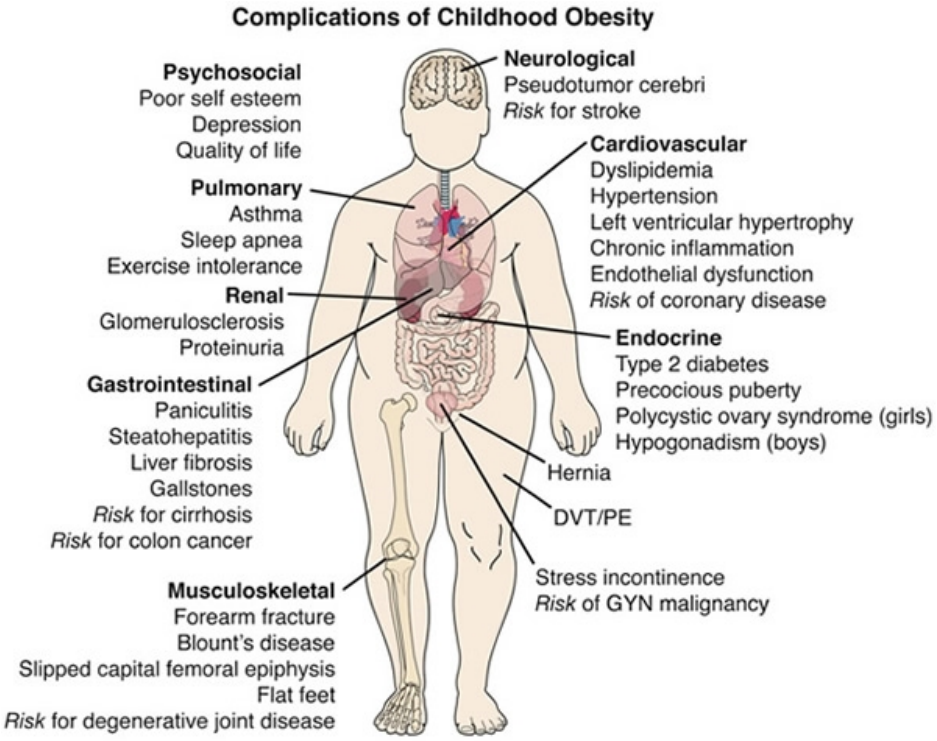
- Prevention of co-morbidities, other benefits, including weight maintenance
- Lustig (UCSF): low-CHO diet can be used to “jump-start” efforts in some patients
- <u>Marci Serota</u>, speaker, RDN, & parent!
- Ensure adequate vitamin D3
- CHOP Healthy Weight Program collaboration



Comorbidities

Individualized monitoring:

- Incidence and severity of fatty liver may be increased
- Disrupted circadian phase may impair sleep (Dr. Xanthopoulous)
- Excess rate of mental health problems (Dr. Hocking)



Hoffman et al, Eur J Endo, 2015 (PMID: 26088821)
Lee & Bray, Obes Res, 1993 (PMID: 16353333)
Roemmler-Zehrer et al., Clin Endo, 2015 (PMID: 24923438)

Exploring integrative health:

- Mindfulness
- Acupuncture
- Aromatherapy
- Yoga
- Others

Dr. Maria Mascarenhas

INTEGRATIVE HEALTH FAMILY EDUCATION DAY

Integrative Approaches to Pain Management

Join us for this half-day symposium for adolescents, parents and caregivers to learn about integrative approaches to pediatric pain management.

SUNDAY, APRIL 7, 2019

Noon — 5 p.m.

Ruth and Tilstram Colket Jr. Translational Research Building on the Raymond G. Perelman Campus

3501 Civic Center Blvd.

Ground floor conference rooms

Philadelphia, PA 19104

Complimentary parking will be available in the Passyunk Garage for Advanced Pediatric Care Parking.

Today, many families are looking for a comprehensive approach to health and wellness. Integrative Healthcare focuses on the whole child, not just on disease prevention and treatment. The potential complementary care fields of mindfulness, aroma therapy, acupuncture, etc. (with traditional medical management) has been proven to reduce stress, speed healing and improve functioning.

Using a variety of treatment approaches allows collaborative providers to identify which strategies are most effective in managing pain. Patients and caregivers learn new skills to support their child's efforts.

REGISTRATION INFORMATION

There is a non-refundable registration fee of $10 per family. Registration is required for each member of the party who will attend. There will be no childcare available so this event is restricted to attendees 12 years and older. Snacks will be provided.

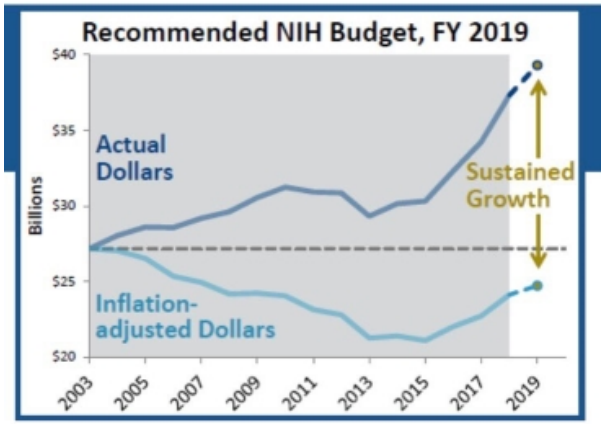
If the registration fee causes a financial burden, please email integrativehealth@email.chop.edu. Kindly RSVP by Monday, March 25, 2019 at integrative-health.eventbrite.com.

Children's Hospital of Philadelphia

Integrative Health

Advocacy & Research Priorities

- *Example:* 21st Century Cures Act for rare disease research, most of this through NIH & FDA



- *Example:* Patient-centered Outcomes Research Institute

pcori® Patient-Centered Outcomes Research Institute

- *Example:* ICD10 diagnostic codes

Take-Home Points

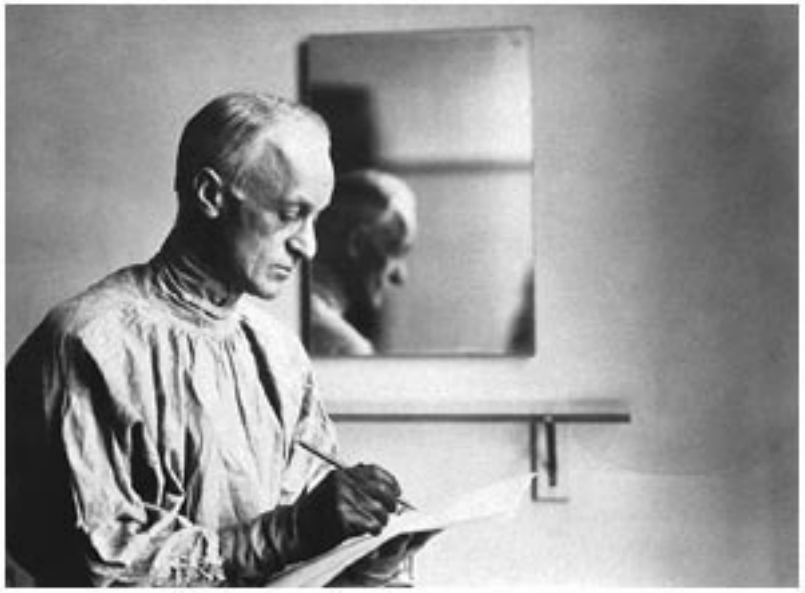
- Prevention (avoiding damage) works best.
- Combination of individualized nutrition, exercise, targeted therapies, therapy for “exogenous” obesity may help, and integrative care can help.
- Consider research opportunities and metabolic surgery.
- Partner with care, research, & advocacy teams!

Additional

Isn't all obesity hypothalamic?

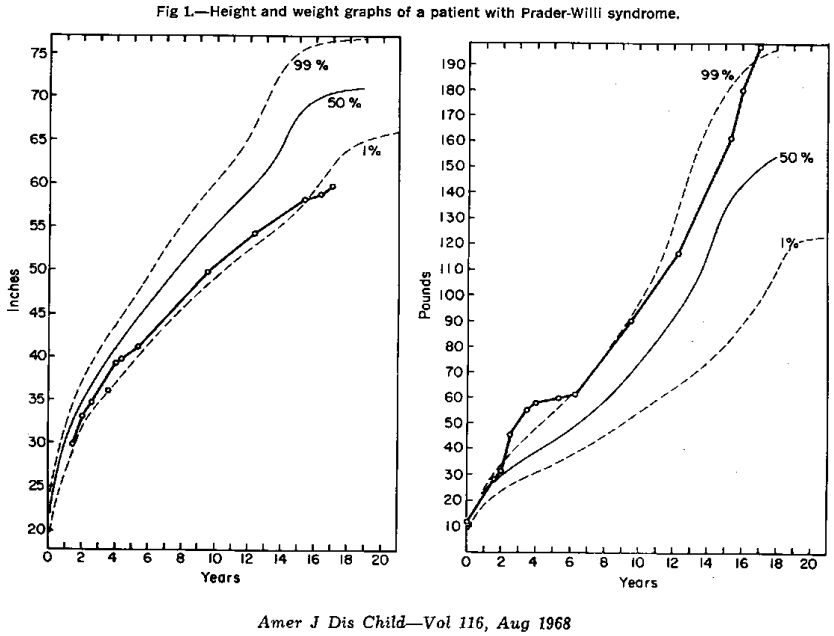
"Here [in the hypothalamus] lies the very main-spring of primitive existence – vegetative, emotional, reproductive – on which with more or less success, man has come to impose a cortex of inhibitions."

Harvey Cushing, 1929



Cited in: Brooks CM, Brain Res Bulletin 1988 (PMID: 3044517)
Photo Credit: NEJM 2006

Example: Prader-Willi Syndrome



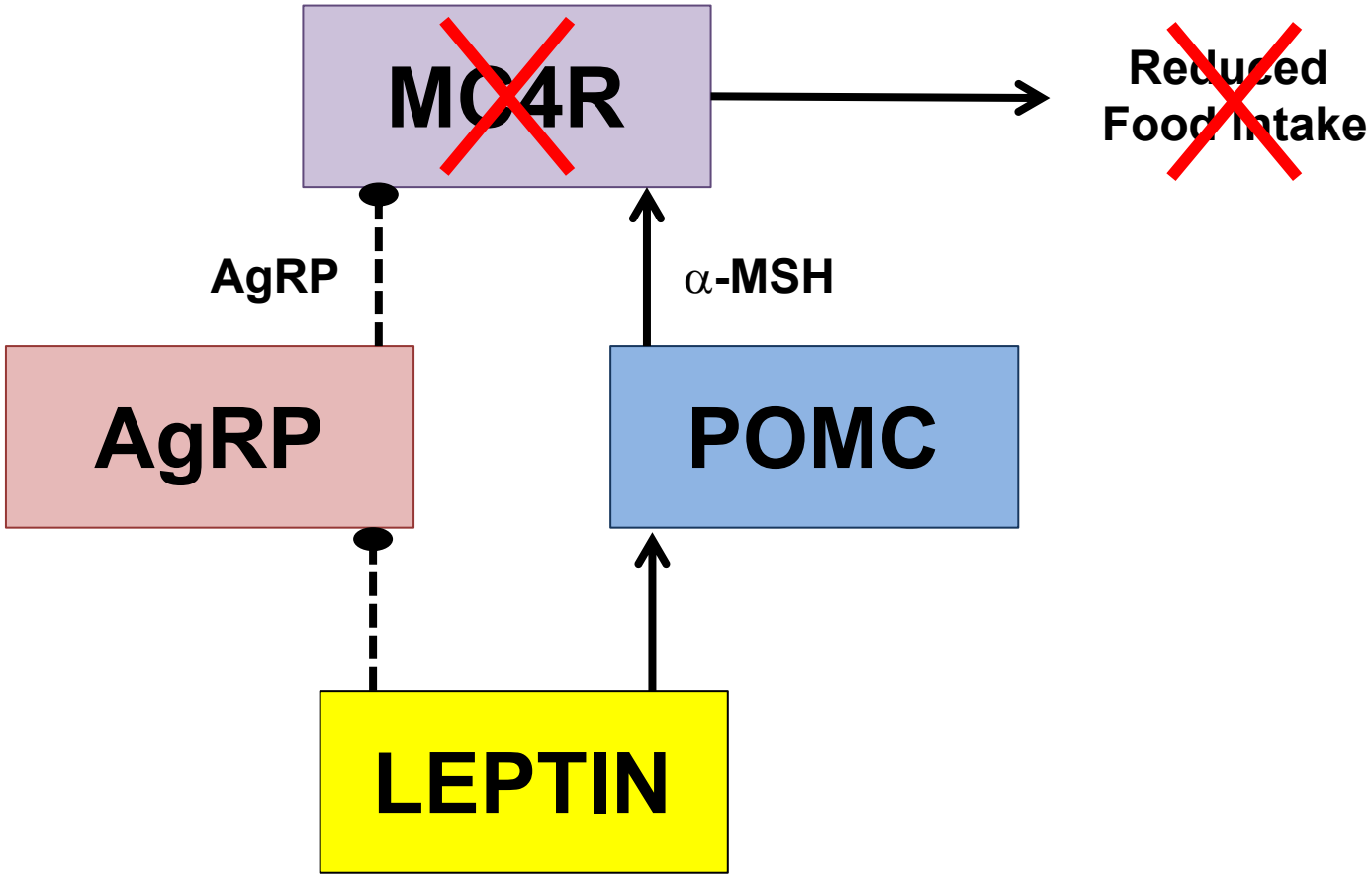
Ladwirth *et al.*, JAMA Pediatrics 1968 (PMID: 5659301)

- First described by Prader, Labhart, and Willi in 1956
- Imprinting defect on chr15q11.2 (deletion of paternal copies)
- Neonatal hypotonia and failure to thrive
- Later: obesity & hyperphagia, intellectual impairment, short stature, hypogonadotropic hypogonadism, small hands/feet
- Value of diagnosis

Example: Melanocortin-4 Receptor Pathway Defects

HYPOTHALAMUS

~3% of severe, early-onset obesity cases: heterozygous mutations in MC4R



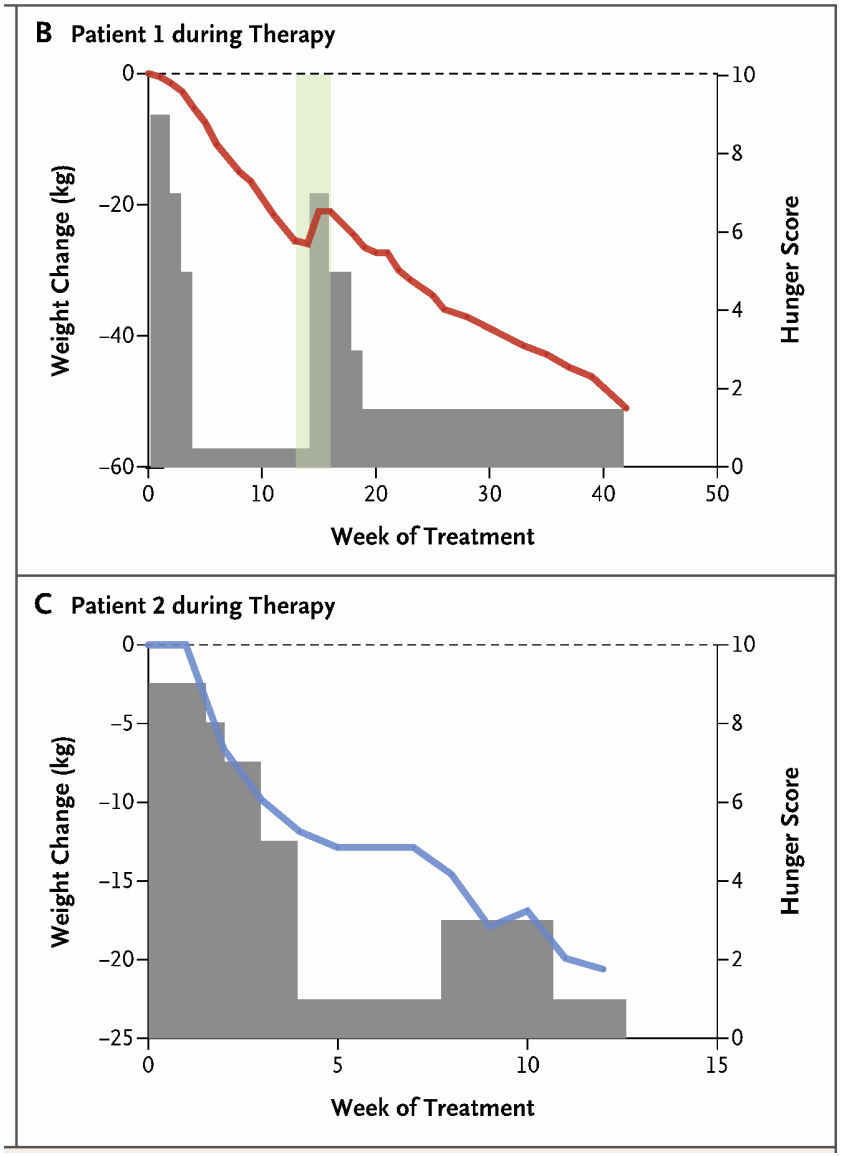
Melanocortin-4 Receptor Agonist

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist

Peter Kühnen, M.D., Karine Clément, M.D., Ph.D., Susanna Wiegand, M.D., Oliver Blankenstein, M.D., Keith Gottesdiener, M.D., Lea L. Martini, M.D., Knut Mai, M.D., Ulrike Blume-Peytavi, M.D., Annette Grüters, M.D., and Heiko Krude, M.D.



Melanocortin-4 Receptor Agonist

ARTICLE IN PRESS

Brief Communication

MOLECULAR METABOLISM

Evaluation of a melanocortin-4 receptor (MC4R) agonist (Setmelanotide) in MC4R deficiency

Tinh-Hai Collet [1,2,12], Béatrice Dubern [3,4,12], Jacek Mokrosinski [1,12], Hillori Connors [5,12], Julia M. Keogh [1], Edson Mendes de Oliveira [1], Elana Henning [1], Christine Poitou-Bernert [3,4], Jean-Michel Oppert [3,4], Patrick Tounian [3,4], Florence Marchelli [3], Rohia Alili [3,4], Johanne Le Beyec [6,7,8], Dominique Pépin [6], Jean-Marc Lacorte [3,4,6], Andrew Gottesdiener [5], Rebecca Bounds [1], Shubh Sharma [5], Cathy Folster [5], Bart Henderson [5], Stephen O'Rahilly [1], Elizabeth Stoner [5], Keith Gottesdiener [5], Brandon L. Panaro [9,10], Roger D. Cone [10,11], Karine Clément [3,4,***,12], I. Sadaf Farooqi [1,*,12], Lex H.T. Van der Ploeg [5,**,12]

Setmelanotide produced weight loss in MC4R heterozygotes and obese controls.

Sponsored protocol: www.geneticobesity.com