

ENDO 2023

Pediatric Endocrinology post-Endo

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PEDIATRIC OBESITY (Session SY012)

- Genetic & Epigenetic (Peter Kuehnen, Charité Berlin)
- Interventions to reduce weight (Alaina Vidmar, Keck School, USC, LA)
- Interventions to reduce NAFLD (Miriam Vos, Emory)

PEDIATRIC OBESITY (Session SY012)

Monogenetic & Epigenetic

- Dysmorphisms
- Other clinical features :
 - Renal dysgenesis
 - Retinitis pigmentosa
 - Polydactyilia
 - Developmental delay
 - Hypogonadism

HYPERPHAGIA +++

Polygenic / Environment

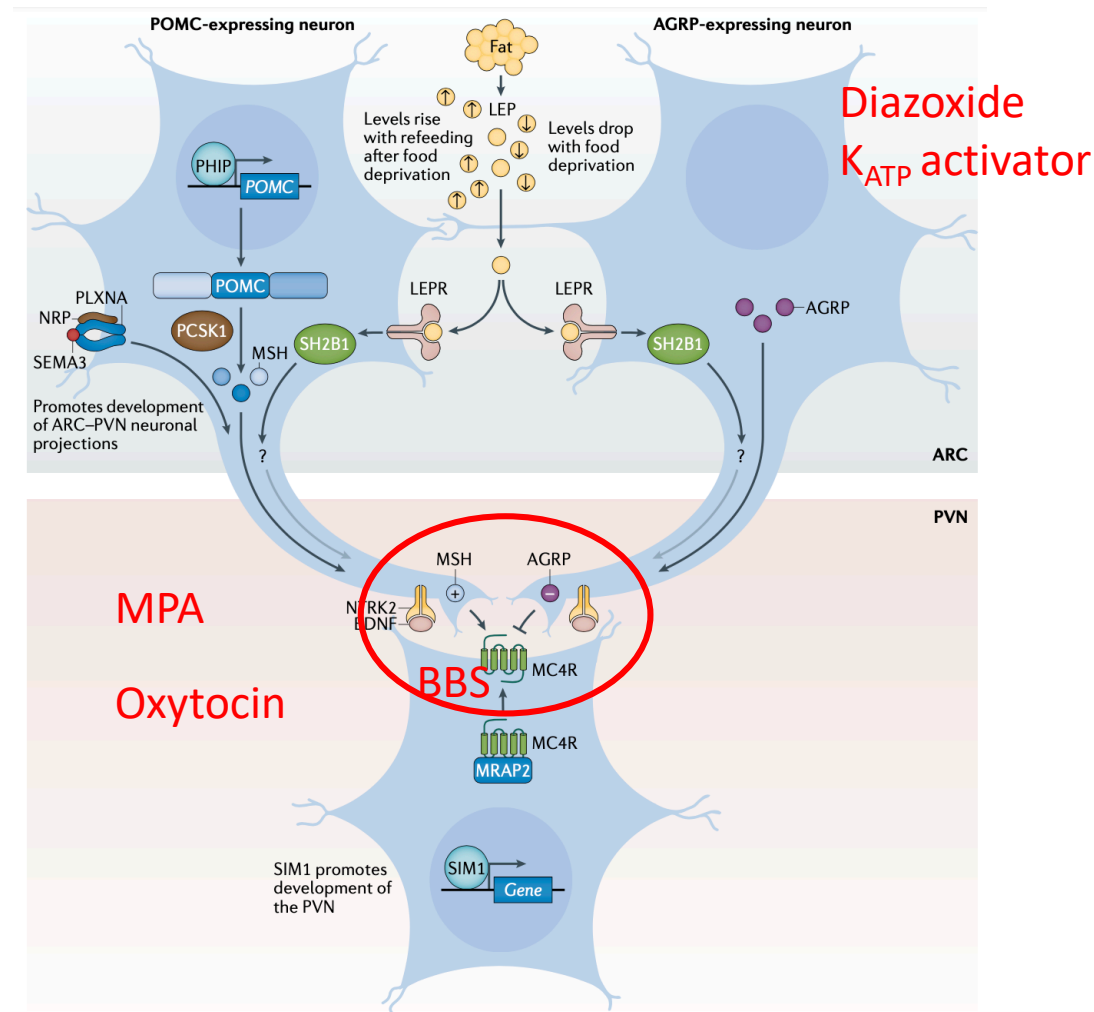
- No dysmorphisms
- Other clinical signs :
metabolic syndrome

LACK OF SATIETY

PEDIATRIC OBESITY (Session SY012) : Translational Medicine

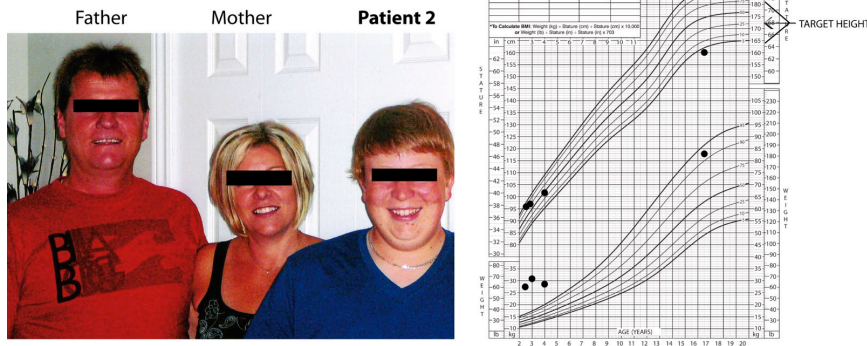
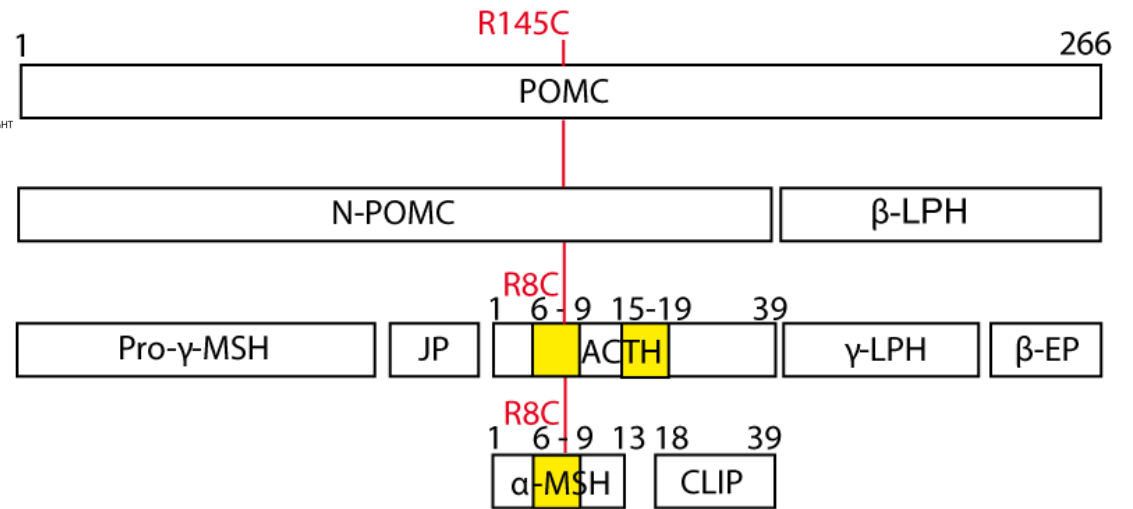
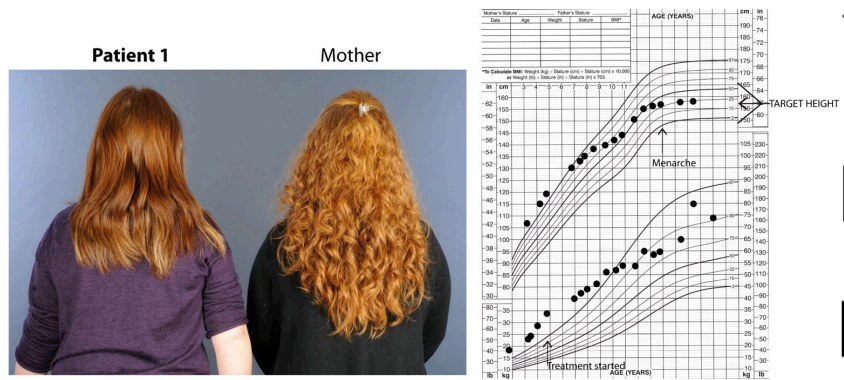
GENETIC

- 70% (47-90%) of weight concordance between MZ twin, 35-45% DZ-twin
- Monogenic obesity : *LEP*, *LEPR*, *POMC*, *PCSK1*, *MC4R*, *BBS1*, *BBS10* – rare, large effect size
- GWAS : BMI associated with common variants close to *FTO* (Frayling, Science 2007) – common , low effect size
- Epigenetic : methylation *POMC*, *HIF3A*



PEDIATRIC OBESITY (Session SY012) : Translational Medicine

GENETIC :POMC deficiency / ACTH bioinactivity



RECEPTORS	SITES OF EXPRESSION	KNOWN PHYSIOLOGICAL EXPRESSION
MC1-R	melanocytes	pigmentation
MC2-R	adrenal cortex	adrenocortical steroidogenesis
MC3-R	CNS, GI tract, kidney	Energy homeostasis, natriuresis
MC4-R	CNS	Energy homeostasis, erectile function
MC5-R	Exocrine cells	Synthesis and secretion of exocrine gland products

PEDIATRIC OBESITY (Session SY012) : Translational Medicine Our option : MPA ?


Received: 11 March 2019 | Revised: 31 July 2019 | Accepted: 24 August 2019

DOI: 10.1111/ijpo.12577

ORIGINAL RESEARCH

pediatricobesity WILEY

Methylphenidate in children with monogenic obesity due to *LEPR* or *MC4R* deficiency improves feeling of satiety and reduces BMI-SDS—A case series

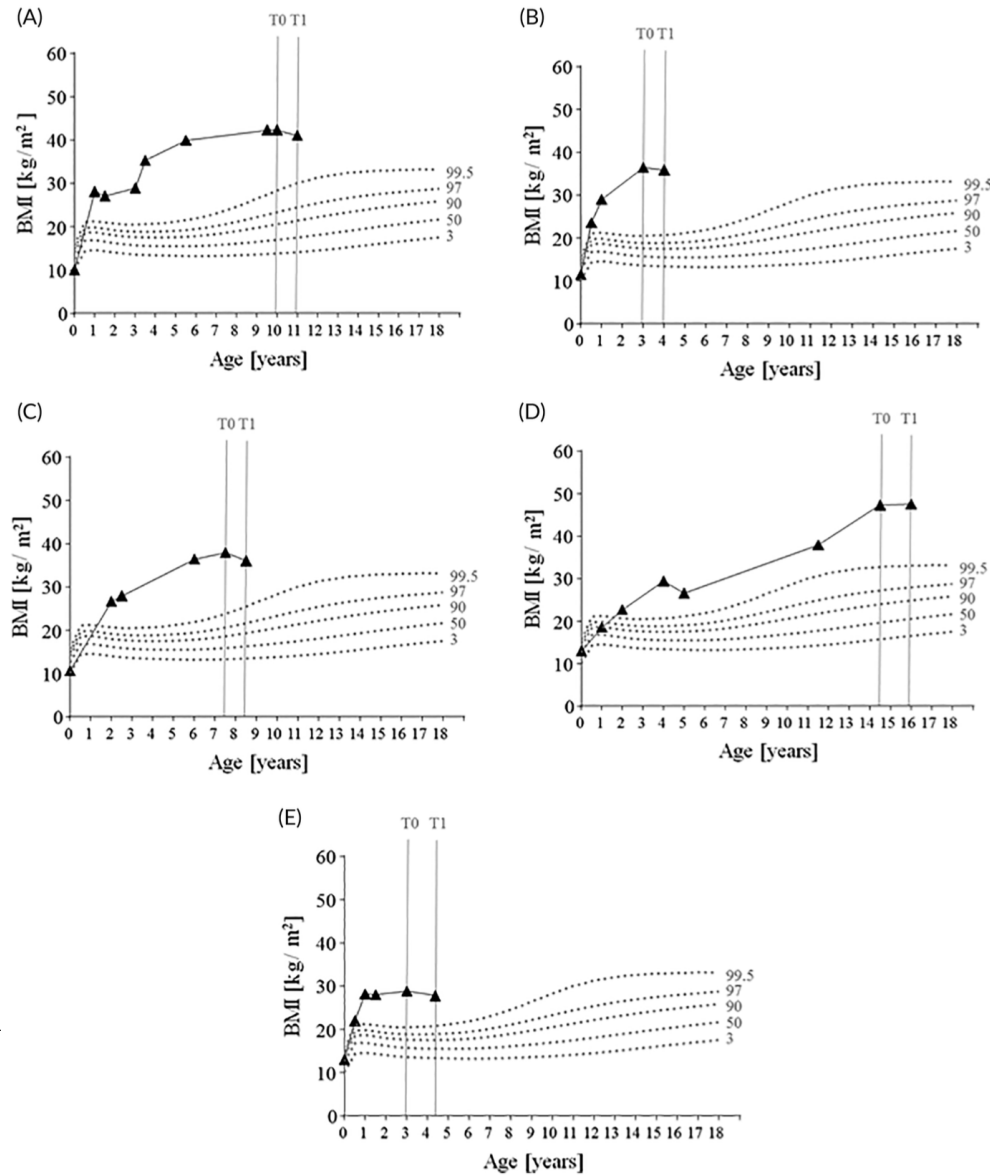
Stephanie Brandt¹  | Julia von Schnurbein¹ | Belinda Lennerz^{1,2} | Katja Kohlsdorf¹ |
Heike Vollbach^{1,3} | Christian Denzer¹ | Harald Bode⁴ | Johannes Hebebrand⁵ |
Martin Wabitsch¹

Methylphenidate in children with monogenic obesity due to *LEPR* or *MC4R* deficiency improves feeling of satiety and reduces BMI-SDS—A case series

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PEDIATRIC OBESITY (Session SY012) : Translational Medicine

Our option : MPA ?



PEDIATRIC OBESITY (Session SY012) : Translational Medicine

The NEW ENGLAND JOURNAL of MEDICINE

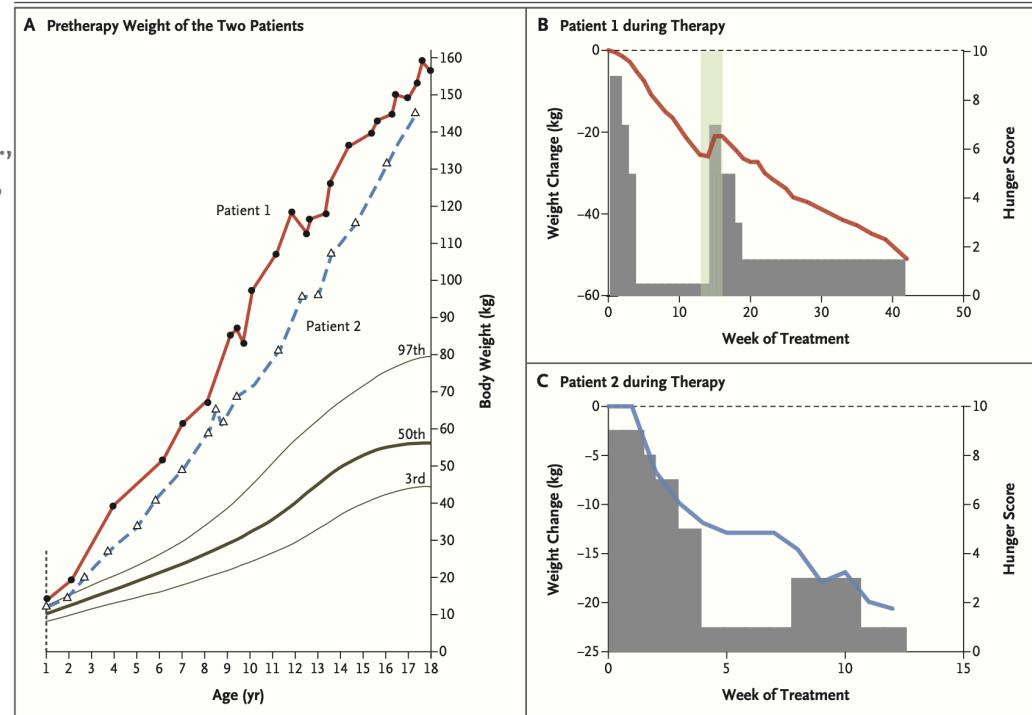
BRIEF REPORT

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.

NEJM, 2016; 375:240-6, 21 July 2016

MC4R Agonist = setmelatoninide



PEDIATRIC OBESITY (Session SY012) : Translational Medicine

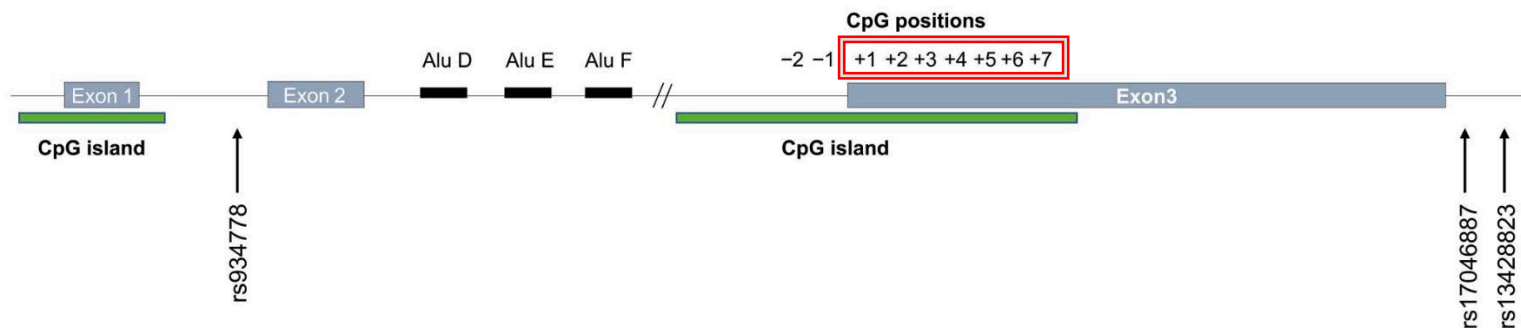
Early-set POMC methylation variability is accompanied by increased risk for obesity and is addressable by MC4R agonist treatment

Lara Lechner¹, Robert Opitz², Matt J. Silver³, Philipp M. Krabusch¹, Andrew M. Prentice³, Martha S. Field⁴, Harald Stachelscheid⁵, Elsa Leitão⁶, Christopher Schröder⁶, Valeria Fernandez Vallone⁵, Bernhard Horsthemke⁶, Karl-Heinz Jöckel⁷, Børge Schmidt⁷, Markus M. Nöthen⁸, Per Hoffmann⁸, Stefan Herms⁸, Patrick W. Kleyn⁹, Matthias Megges¹, Ulrike Blume-Peytavi¹⁰, Katja Weiss¹¹, Knut Mai^{12,13}, Oliver Blankenstein^{1,14}, Benedikt Obermayer¹⁵, Susanna Wiegand¹⁶, Peter Kühnen^{1*}

Lechner et al., *Sci. Trans. Med.*, eadg1659 (2023), 19 July 2023

EPIGENETIC OBESITY RISK VARIANT in *POMC* gene

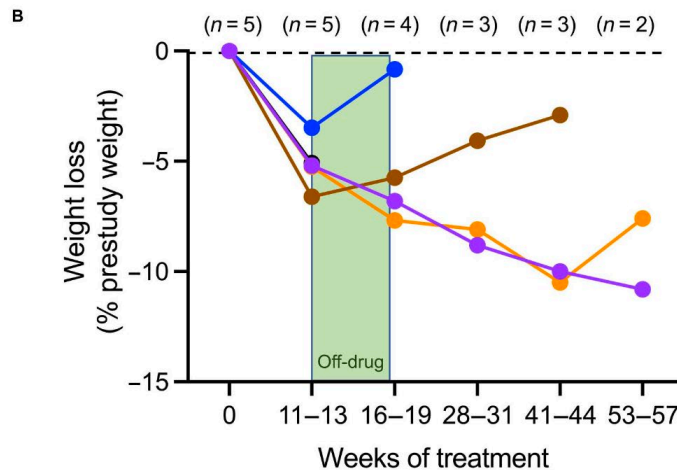
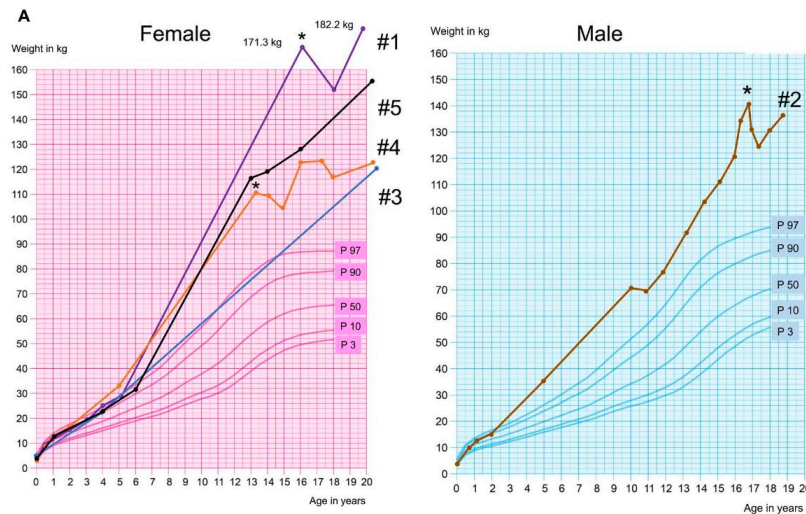
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PEDIATRIC OBESITY (Session SY012) : Translational Medicine

Lechner et al., *Sci. Trans. Med.*, eadg1659 (2023), 19 July 2023

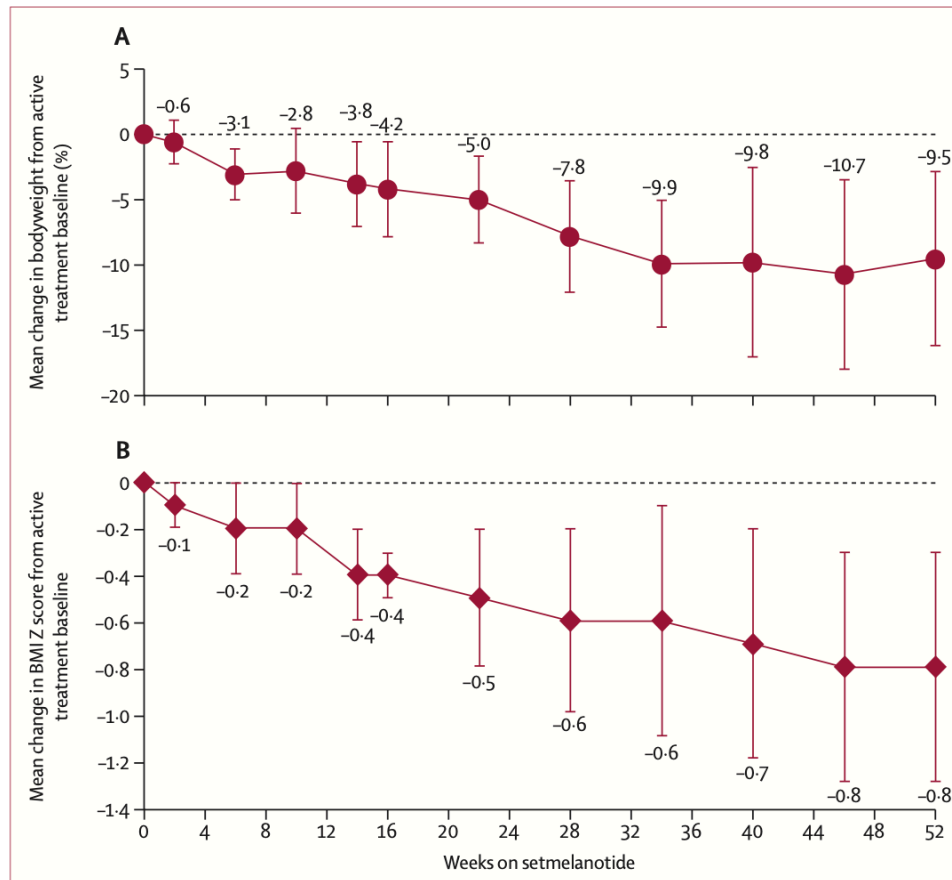
EPIGENETIC OBESITY RISK VARIANT in *POMC* gene



PEDIATRIC OBESITY (Session SY012) : Translational Medicine

Haqq et al., Lancet Diabetes Endocrinol, 2022

Setmelatonide , 1-3 mg sc once per day, associated with weight reduction of 9.5% over 1 yr in **BBS**



PEDIATRIC OBESITY (Session SY012) : Translational Medicine
--- add on. «**ADJUVANT TX**»

**Intranasal Carbetocin Reduces Hyperphagia, Anxiousness,
and Distress in Prader-Willi Syndrome: CARE-PWS
Phase 3 Trial**

Elizabeth Roof,¹ Cheri L. Deal,²  Shawn E. McCandless,³  Ronald L. Cowan,⁴  Jennifer L. Miller,⁵ *et al.*

JCEM, 2023, 108: 1696-1708

- objective : LA oxytocin safety in PWS
- participants : 130
- design: RCT – double blind – placebo controlled – phase 3 trial
- interventions : placebo vs carbetocin 9.6 mg/dose or 3.2 mg/dose, 3 times daily for 8w (PCP), then 56 w FU placebo assigned randomly to either 9,6 or 3,2 mg regimen.
- primary endpoints: hyperphagia, obsessive-compulsive behavior
- secondary endpoints : anxiousness

Study performed during COVID 19 pandemics

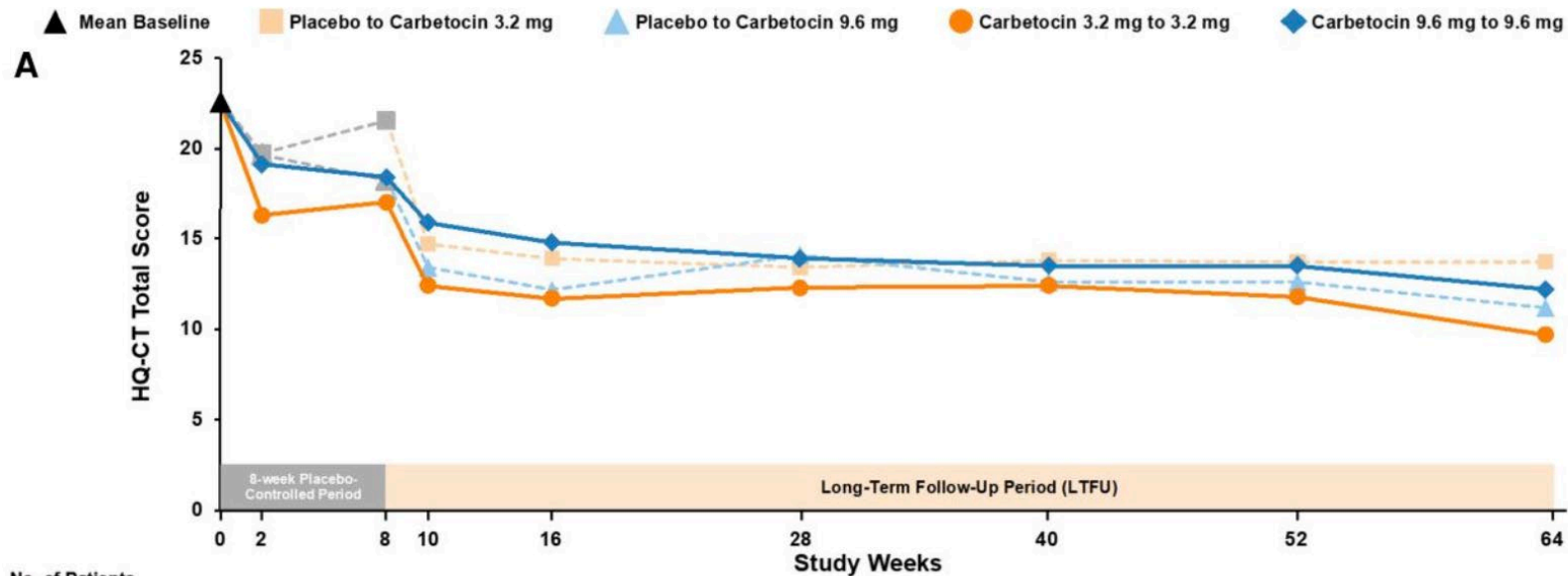
PEDIATRIC OBESITY (Session SY012) : Translational Medicine --- add on

Intranasal Carbetocin Reduces Hyperphagia, Anxiousness, and Distress in Prader-Willi Syndrome: CARE-PWS Phase 3 Trial

JCEM, 2023, 108: 1696-1708

Elizabeth Roof,¹ Cheri L. Deal,² Shawn E. McCandless,³ Ronald L. Cowan,⁴ Jennifer L. Miller,⁵

HYPERPHAGIA



NO EFFECT ON WEIGHT

PEDIATRIC OBESITY (Session SY012) : Translational Medicine
--- add on. «**ADJUVANT TX**»

Diazoxide Choline Extended-Release Tablet in People With Prader-Willi Syndrome: A Double-Blind, Placebo-Controlled Trial

Jennifer L. Miller,^{1,*}  Evelien Gevers,^{2,*} Nicola Bridges,³ Jack A. Yanovski,⁴ Parisa Salehi,⁵ *et al.*

JCEM, 2023, 108: 1676-1685

- objective : assess Diazoxide Choline ER (DCCR) effect on hyperphagia
- participants : 127
- design: RCT – double blind – placebo controlled – phase 3 trial
- interventions : DCCR vs placebo (2:1) x 13 w .
- primary endpoints: hyperphagia. : NO EFFECT
- secondary endpoints : body composition : slightly effect

Study performed during COVID 19 pandemics

PEDIATRIC OBESITY (Session SY012)

Treatment options / non-syndromic obesity

GLP1RA (liraglutide / semaglutide)

ORIGINAL ARTICLE

A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity

Aaron S. Kelly, Ph.D., Pernille Auerbach, M.D., Ph.D., Margarita Barrientos-Perez, M.D.,
Inge Gies, M.D., Ph.D., Paula M. Hale, M.D., Claude Marcus, M.D., Ph.D.,
Lucy D. Mastrandrea, M.D., Ph.D., Nandana Prabhu, M.Sc.,
and Silva Arslanian, M.D., for the NN8022-4180 Trial Investigators*

NEJM, 2020; 382:2117-28

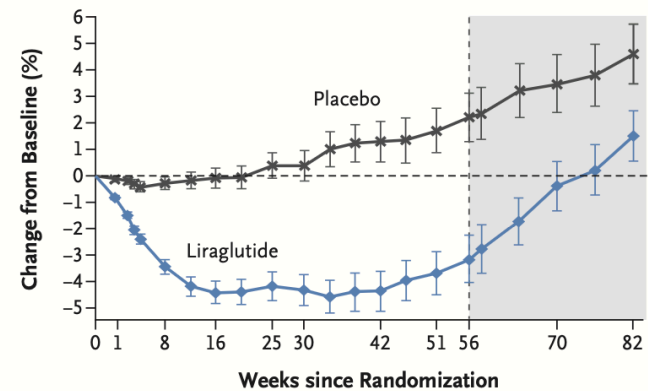
Once-Weekly Semaglutide in Adolescents with Obesity

Daniel Weghuber, M.D., Timothy Barrett, Ph.D., Margarita Barrientos-Pérez, M.D.,
Inge Gies, Ph.D., Dan Hesse, Ph.D., Ole K. Jeppesen, M.Sc., Aaron S. Kelly, Ph.D.,
Lucy D. Mastrandrea, M.D., Rasmus Sørrig, Ph.D., and Silva Arslanian, M.D.,
for the STEP TEENS Investigators*

ABSTRACT

NEJM, 2022; 387:2245-57

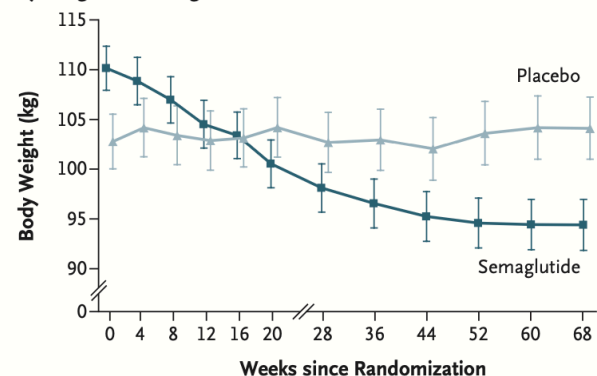
F Relative Change in Body Weight



No. of Participants

Placebo	126	125	123	116	116	105	101	105	97	102
Liraglutide	125	123	119	118	119	110	107	113	106	112

F Body Weight According to Weeks since Randomization



No. of Participants

Placebo	67	62	63	59	66	64	64	63	61	64	63	62
Semaglutide	134	122	127	121	132	128	133	131	131	131	131	131

PEDIATRIC OBESITY (Session SY012)

Treatment options / non-syndromic obesity

Phentermine / Topiramate

ORIGINAL ARTICLE

Phentermine/Topiramate for the Treatment of Adolescent Obesity

Aaron S. Kelly, Ph.D.,¹ Megan O. Bensenior, M.D.,¹ Daniel S. Hsia, M.D.,² Ashley H. Shoemaker, M. Craig Peterson, M.S.,⁴ and Santosh T. Varghese, M.D.,⁴ for the Trial Investigators*

Phentermine : side effect anxiety,
CI cardiac valve disease, dependence,
FDA > 16 yr

Topiramate: suppress appetite, GABA ergique.
Side effect: paresthesia, mood changes

Antiepileptica, used also in cases of R-OH
addiction

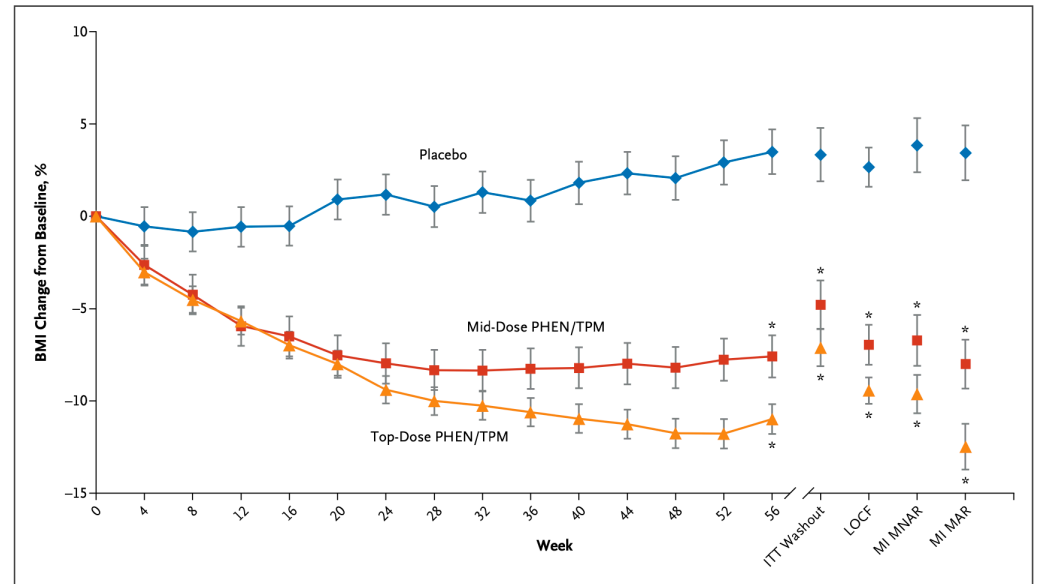


Figure 2 Percent Body-Mass Index Change Over Time.

Plot of least square means (\pm SE) of percentage change in body-mass index (BMI) using observed data from baseline to week 56 by treatment group (with the primary analysis, modified intent-to-treat [ITT], and other imputation models). The mid and top doses are 7.5 mg/46 mg and 15 mg/92 mg of phentermine/topiramate (PHEN/TPM), respectively. LOCF denotes last observation carried forward, MAR missing at random, MI multiple imputation, and MNAR, missing not at random. * $P < 0.001$ versus placebo.

Thank you