

Weight Gain Crucial for Mental and Somatic Improvement in Anorexia Nervosa: Role of Hypoleptinemia

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Conflict of Interest

- **Funding of metreleptin case studies: Christina Barz Foundation, University of Duisburg-Essen**
- **Named as inventor in 3 patent filings for use of leptin analogs in anorexia nervosa and depression (University of Duisburg-Essen)**
- **Leptin and anorexia nervosa related research funded since 1995 by Deutsche Forschungsgemeinschaft, Bundesministerium für Bildung und Forschung and EU**

Core Phenotype of Anorexia Nervosa

- Features

- Female preponderance
- Circumscribed age range upon manifestation
- Rather homogeneous clinical symptomatology
- Underweight
- Entrapment



Holy Elizabeth

- Intertwining of **primary cognitions and behaviors** with **somatic and psychological sequelae** of starvation

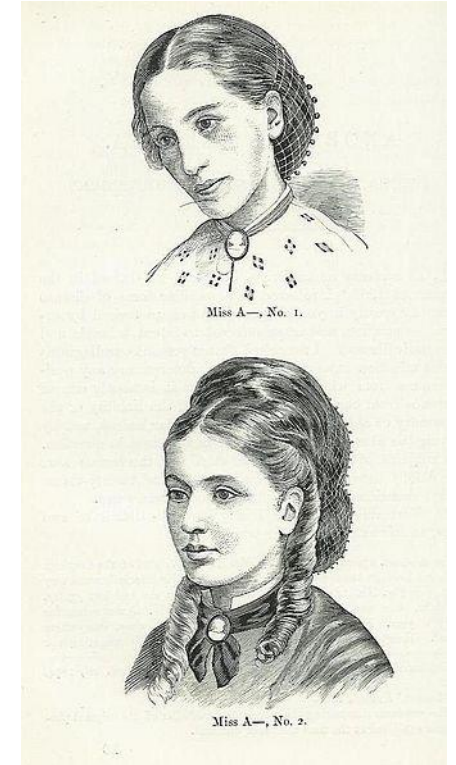
- AN and starvation: overlap of symptoms



Samuel van Hoogstraaten

The Doctors Visit

1670–1736

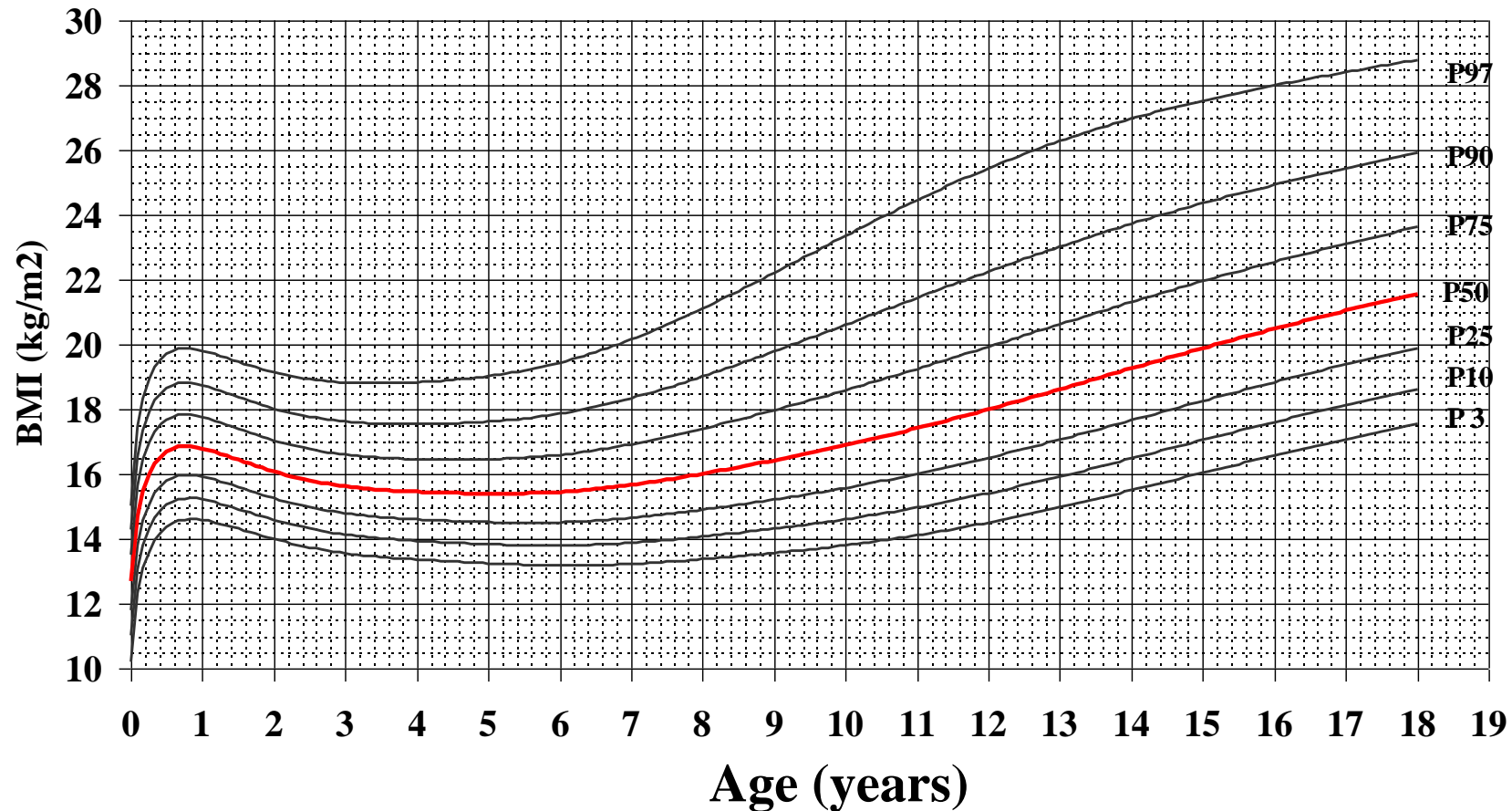


Gull, 1874

Hebebrand et al., J Neural Transm 2004;

Hebebrand and Bulik, Int J Eat Dis 2011

BMI Centiles for Girls



DSM-5
5th centile recommended
as cut-off in children and
adolescents

Hebebrand et al., Int J Eat Dis, 1996

Kromeyer-Hauschild et al., Monatsschrift Kinderheilkunde 2001

Definition of Starvation

- **STARVATION**

- State of having no food for a long period, often causing death
- Severe deficiency in caloric energy intake, below the level needed to maintain an organism's life. Most extreme form of malnutrition.

Anorexia nervosa: Semi-starvation

<https://dictionary.cambridge.org/>

<https://en.wikipedia.org/wiki/Starvation>

Starvation

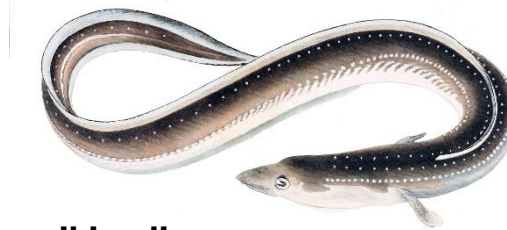
- Continuous physiological adaptations until death
 - Females survive longer and achieve lower BMI
- Species variability in time span between meals
- Frequency / duration of food shortages differ substantially
- Bacteria can switch from energy intake to starvation mode
- Substantial evolutionary adaptations resulted in variability of response to starvation
 - Starvation precludes reproduction
 - Reproduction only after prolonged starvation

1 meal/week

**survival without
food >1 y**



<https://de.wikipedia.org>



**reproduction after
prolonged fast
(>6000 km to
Sargossa sea)**

Progressive Adaptation to Starvation

- **Acute lack of food: strong stress factor**
 - Increased achievement potential
- **Prolonged starvation: chronic stress factor with multiple negative consequences endangering survival**
- **Continuous developmental, physiological and behavioral adaptations**
 - Aim: increase probability of survival
- **Major adaptations**
 - **Gastrointestinal tract: Enable rapid utilization of ingested energy once food is available again**
 - **Maintenance of physiologic functions for important behaviors (physical activity to allow flight or food foraging)**



Treating Anorexia Nervosa

Weight Gain is Crucial

- **Nice Guideline (NG69; updated 2020):**
 - **Key goal: help people to reach a healthy body weight or BMI for age**
 - Weight gain key in supporting other psychological, physical and quality of life changes required for improvement or recovery
- **American Psychiatric Practice Guideline (Crone et al., Am J Psychiatry 2023)**
 - **Medical stabilization, nutritional rehabilitation, weight restoration, and maintenance of weight gain are critical components of treatment for AN that focus on helping the patient achieve and maintain a healthy and medically appropriate weight for their age and height**



Treating Anorexia Nervosa

Weight Gain is Crucial

- **American Psychiatric Practice Guideline**
 - The goals of nutritional rehabilitation (...) are to (...) correct biological and *psychological sequelae of malnutrition*, normalize eating patterns, and achieve normal perceptions of hunger and satiety
 - Weight gain also results in improvements in psychological complications of semistarvation. considerable evidence to suggest that other eating disorder symptoms diminish as weight is restored and maintained

Crone et al., Am J Psychiatry 2023



<https://www.hypnotic-downloads.com/keep-weight-off-after-reaching-your-target>

<https://www.nationaleatingdisorders.org/learn/general-information/recovery>

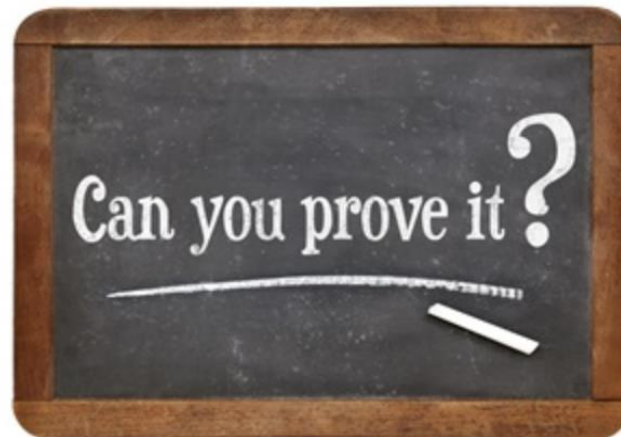
Scant Evidence for Effects of Weight Gain on Psychological Functioning

- Starvation has been shown to lead to depressive symptoms, including low mood, impaired concentration, low energy, and sleep disturbance, as well as increased anxiety and obsessionality (Keys et al. 1950)
- There is considerable evidence to suggest that other eating disorder symptoms diminish as weight is restored and maintained*
 - ...clinical experience indicates that with weight restoration, food choices increase, food hoarding decreases, and obsessions about food decrease in frequency and intensity...*
- Attention, concentration, and other cognitive effects of semistarvation also improve with renourishment*

* no reference provided

Why Scant Evidence Only?

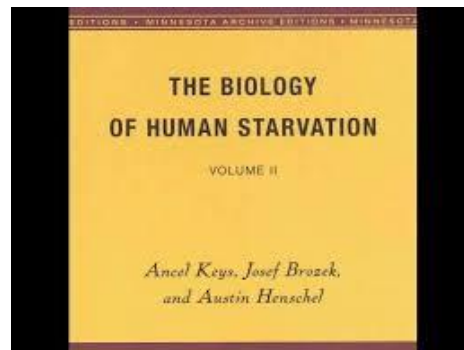
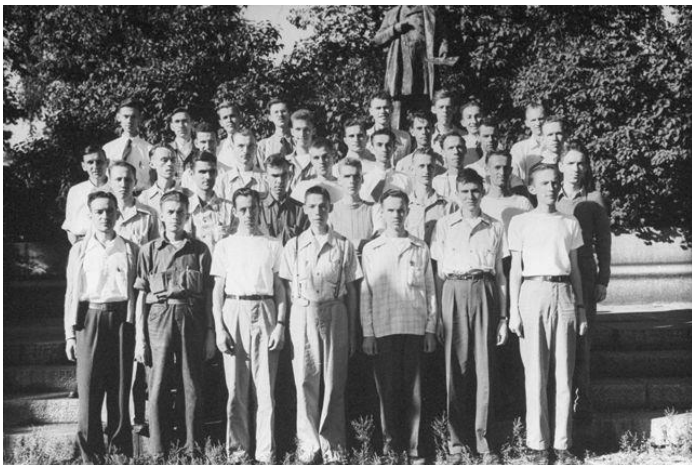
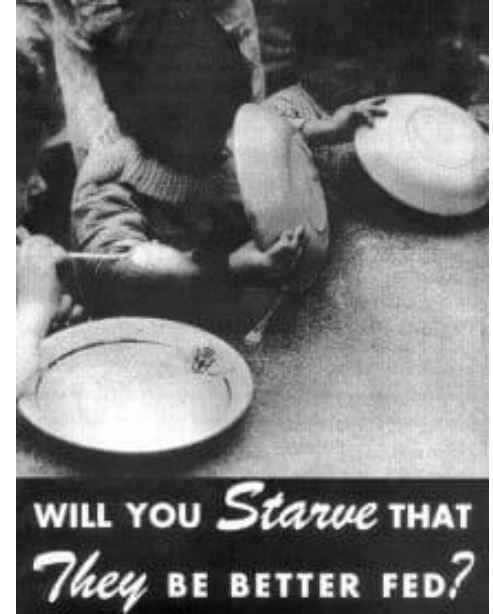
- **Daily clinical experience of improvement with weight gain**
- **Explanations for observed psychopathology**
 - Starvation related
 - AN specific symptoms
 - Premorbid psychopathology
- **Difficult to disentangle effects of weight gain from other effects**
- **Lack of clinical studies aimed at detection of effects of weight gain**



Symptoms Common to both Anorexia Nervosa and Starvation

Minnesota Starvation Experiment

- 1944-1945
- 36 voluntary participants
- 12-wk baseline, 24-wk starvation, 12-wk rehabilitation
- 22 miles of walking/week; defined duties
- Weight loss of 25%
- Detailed somatic and psychological assessments



Keys et al. (1950): *The Biology of Human Starvation*



Ancel Keys

Minnesota Starvation Experiment

Hunger/Appetite/Eating Behavior

„Semi-Starvation Neurosis“

- Preoccupation with thoughts of food

- **Hungry all the time**
- Food topics major focus of conversations and day dreams
- Cookbooks and menus exceedingly important (cook as a vocation)
- Keen awareness of references to food and eating in e.g. movies
- Vivid vicarious pleasure derived from watching other persons eat or from smelling food
- Excessive gum chewing, cigarette smoking increased
- **Individual food dislikes rapidly abandoned**



Life magazine, July 30, 1945

- Eating behavior

- Meals ate silently and deliberately with a total attentional focus on eating
- Consumption of (hot) fluids increased
- Salt and spices used more frequently
- Bulk of food: water added amply (“souping”)

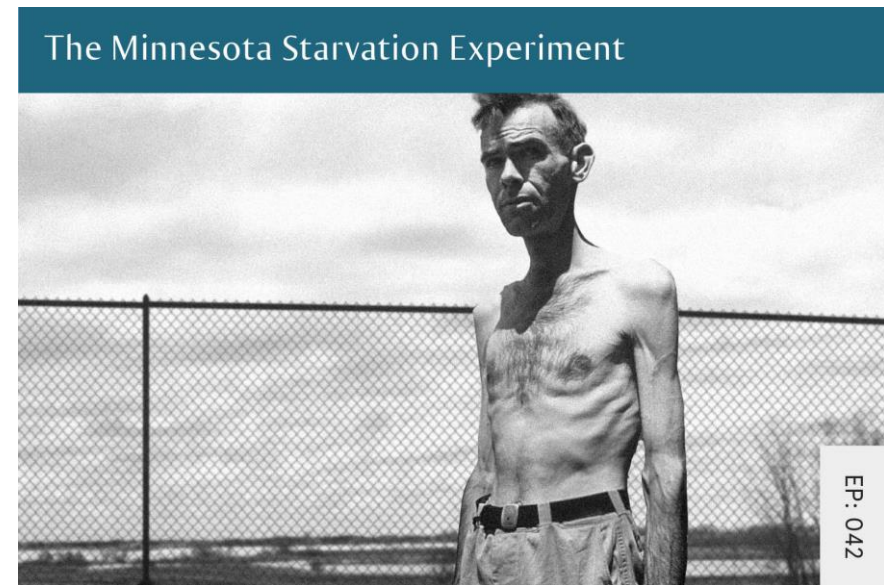
Keys et al. (1950): *The Biology of Human Starvation*

Minnesota Starvation Experiment

Psychological/Behavioural Adaption

„Semi-Starvation Neurosis“

- Tiredness
- Depressed mood
- Increased rigidity
- Reduced
 - Sociability
 - Sexual desire/libido
 - Spontaneity and creativity
 - Concentration and short-term memory
 - **Physical activity**
 - Restlessness
 - Nervousness



Life magazine, July 30, 1945

Self-Ratings of Psychological Items During Minnesota Starvation Experiment

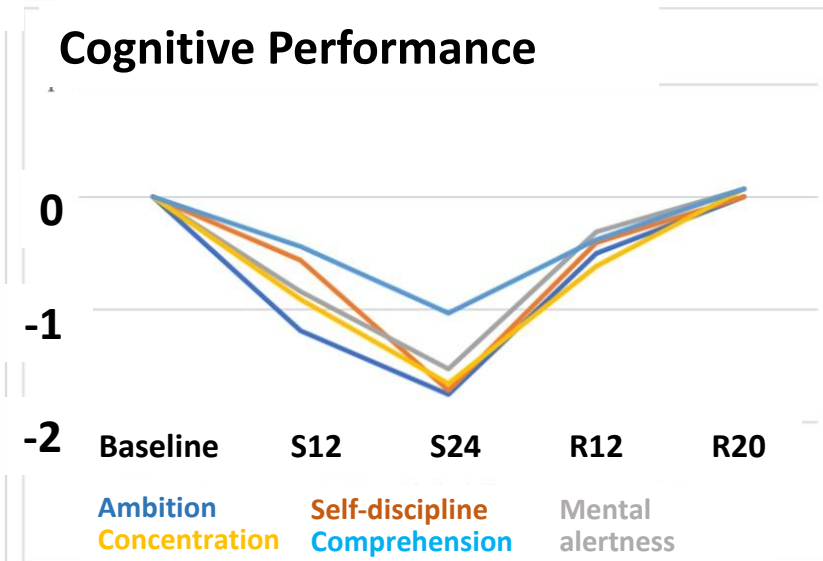
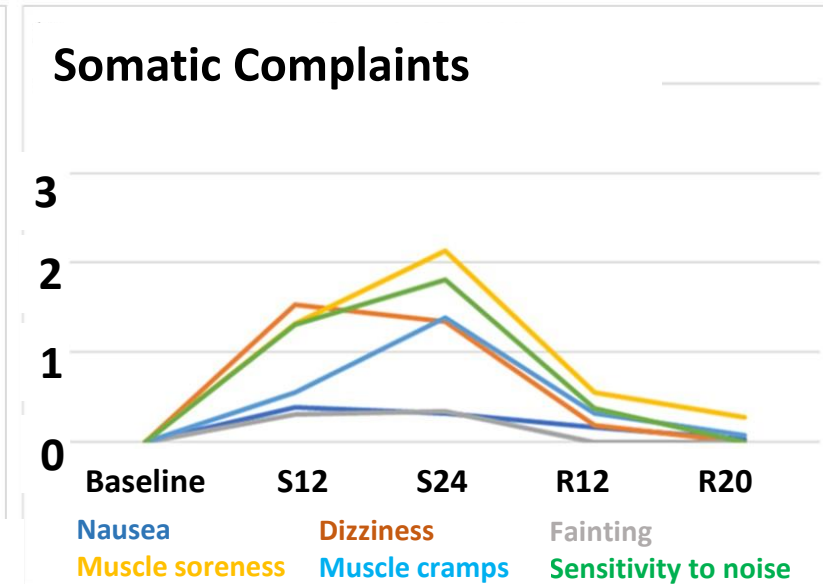
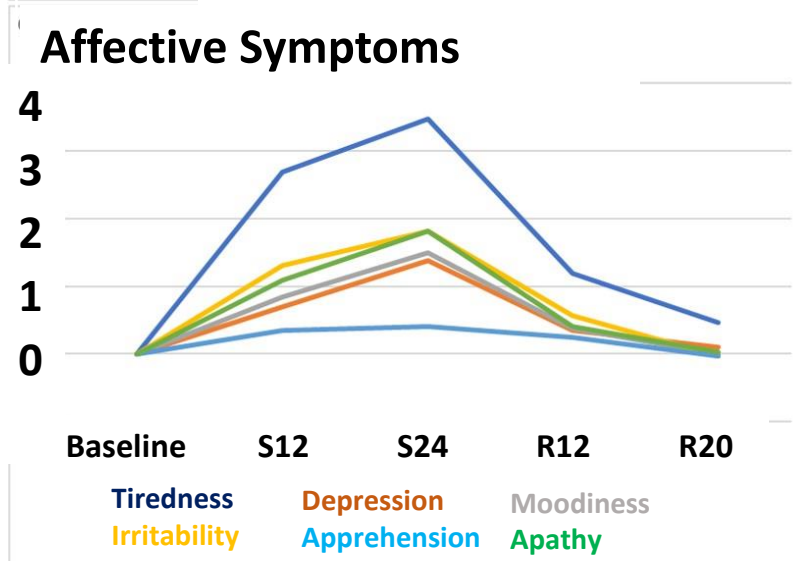
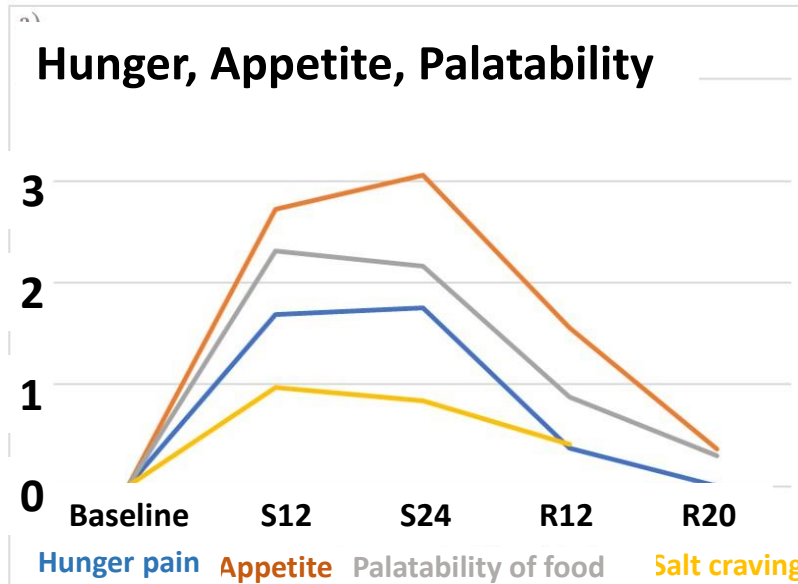
Visual Analog Scale

-5 to +5

1 = more
5 = extremely more

-1 = less
-5 = extremely less

0 = symptom absent



Starvation phase

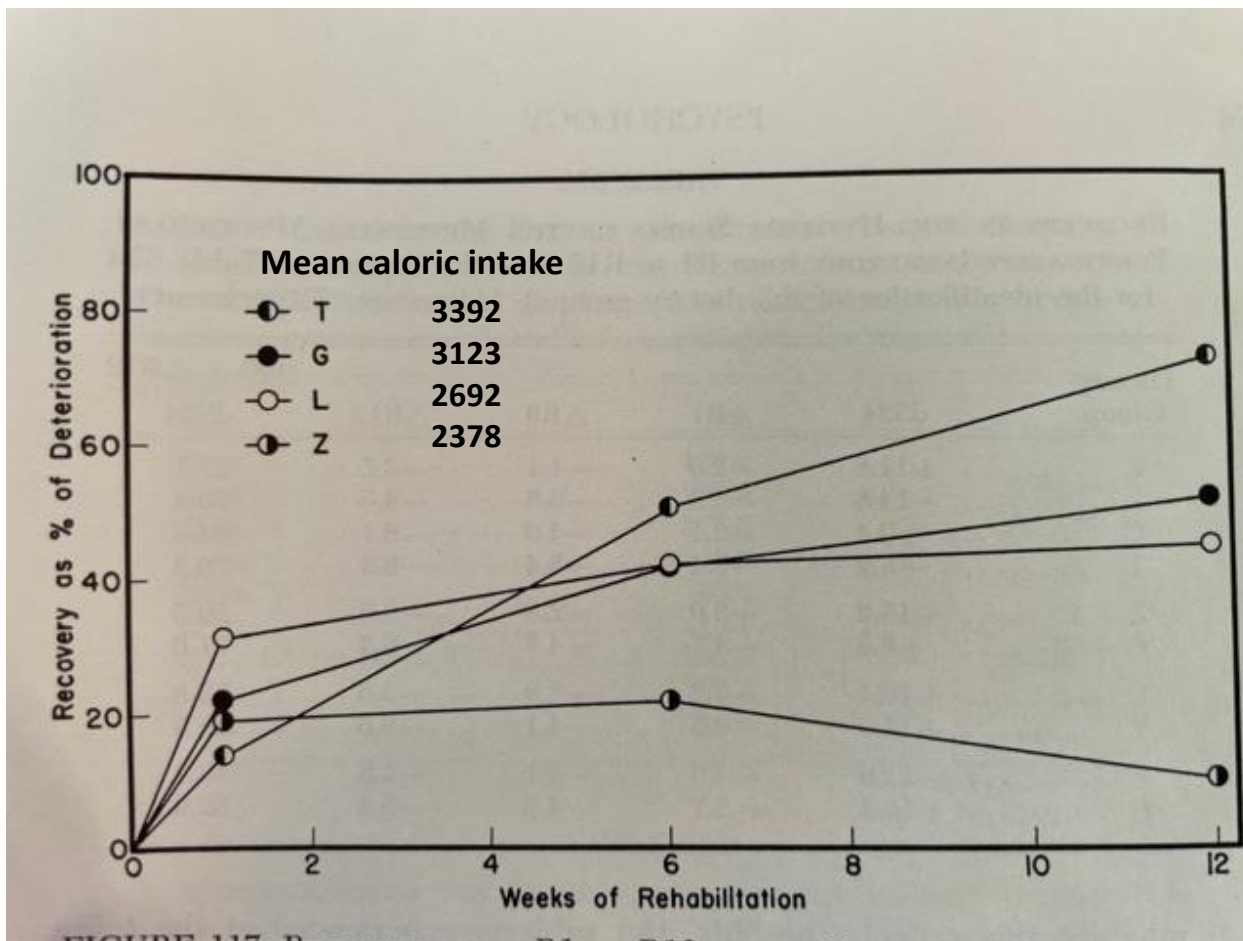
S12
S24

Rehabilitation phase

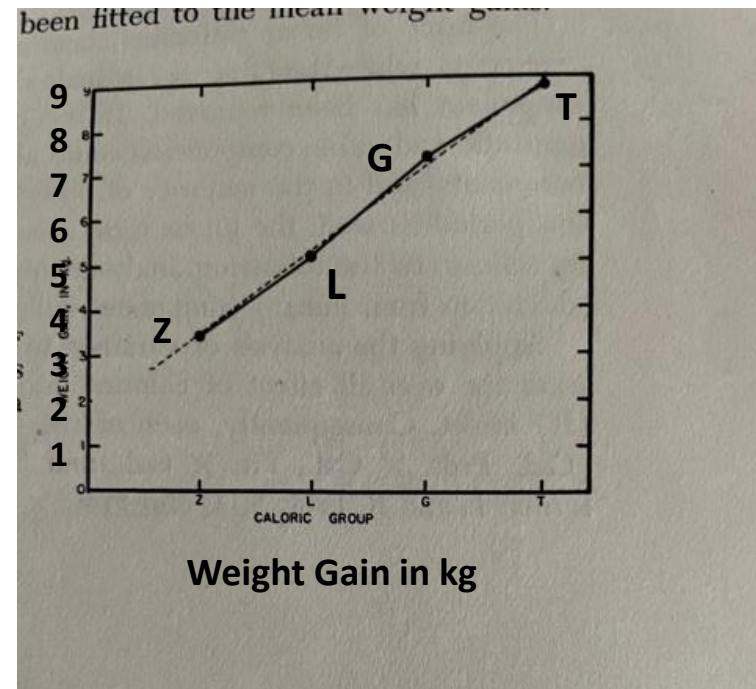
R12
R20

Depression Improves Proportional to Caloric Intake During Rehabilitation Phase

Weeks R1 to R12 – Depression Score of MMPI Subscale – Recovery as % of Deterioration



Keys et al., 1950



How does Weight Gain Lead to Mental Improvement?

- **Direct effects of increased energy intake?**
 - Elevation of energy intake alone not effective
 - If prolonged, inseparable from weight gain
- **Alterations of the microbiome?**
- **Direct and indirect effects of weight gain?**
 - Non-adipose tissue mass
 - Adipose tissue mass

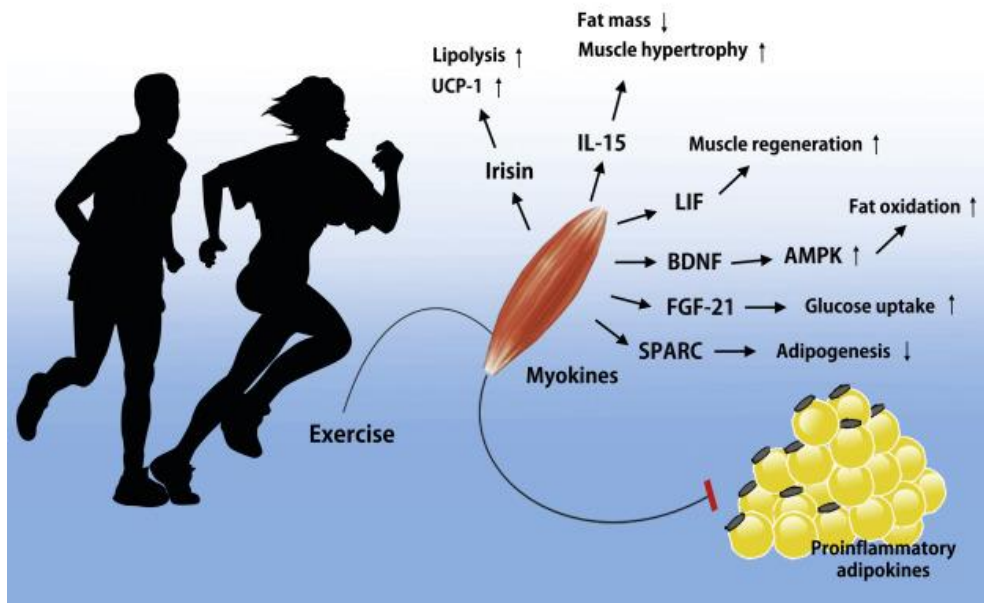
How does Weight Loss Lead to Mental Deterioration?

Weight Loss

Loss in Fat Free Mass and Fat Mass

- **Fat Free Mass**

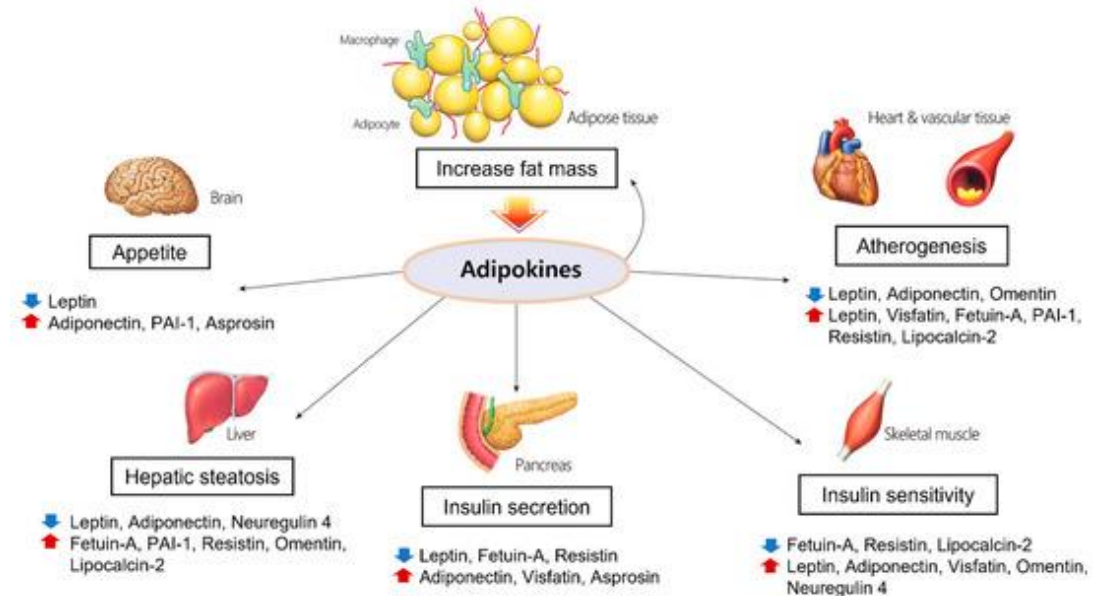
- e.g. brain, liver, bone, muscle
 - e.g. muscle
 - myokines



So et al., Integ Med Research 2014

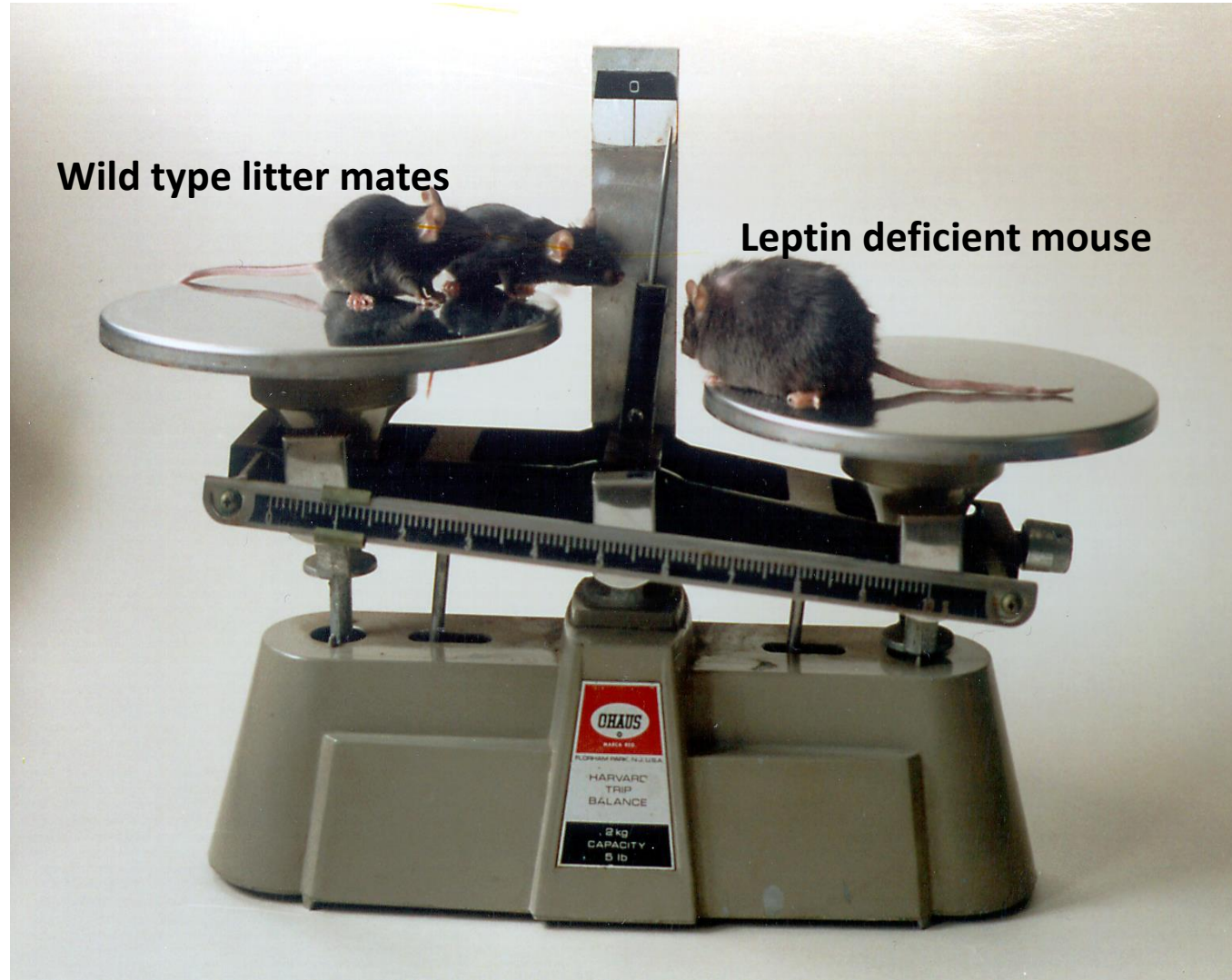
- **Fat Mass**

- largest endocrine tissue
- adipokines
 - e.g. leptin, visfatin, adiponectin
 - > 100 known adipokines



Kim et al., Molecules 2022

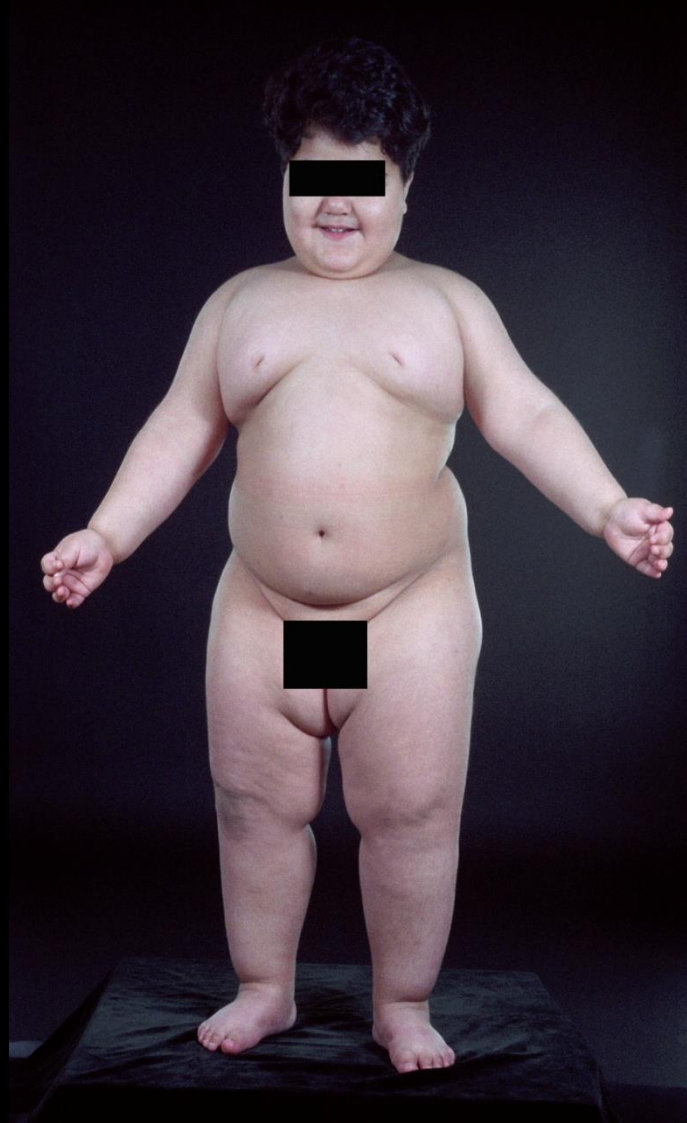
ob/ob Mouse



Congenital Leptin Deficiency

Anorexigenic
hormone?

Satiety
hormone?



Prior to leptin
42 kg at age 3



After leptin treatment
32 kg at age 7

Farooqi et al.,
NEJM 1999

Weight Change after 4 Weeks of Metreleptin Treatment

11 females with hypothalamic amenorrhea

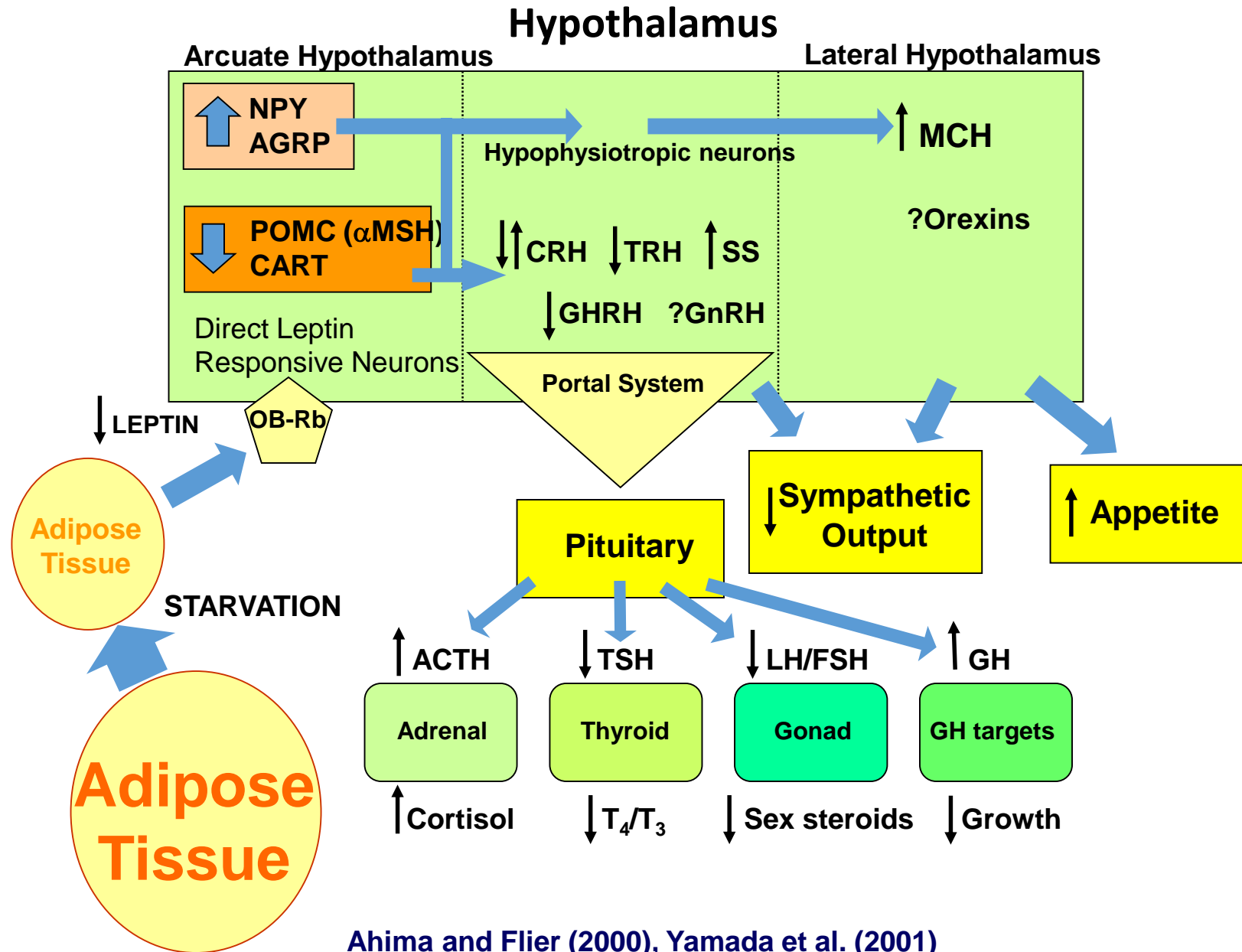
Dosage: 0.08 mg/kg

After 8 weeks: \emptyset -1,1 kg

Chou et al., PNAS 2011

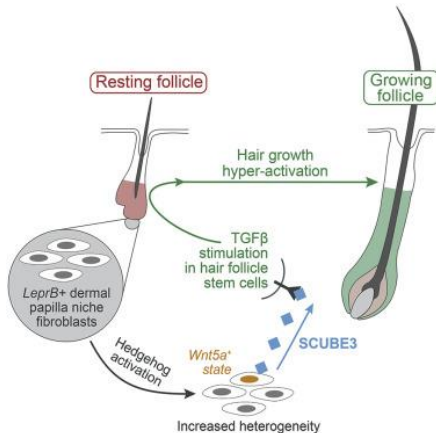
Patient	Weight Change After 4 Weeks
A	-1.1
B	-0.3
C	+0.6
D	-0.6
E	-0.8
F	+1.35
G	-2.25
H	+0.1
I	-1.12
J	+0.8
K	+0.75
\emptyset	-0.23

Leptin Signaling: Adaptation to Starvation

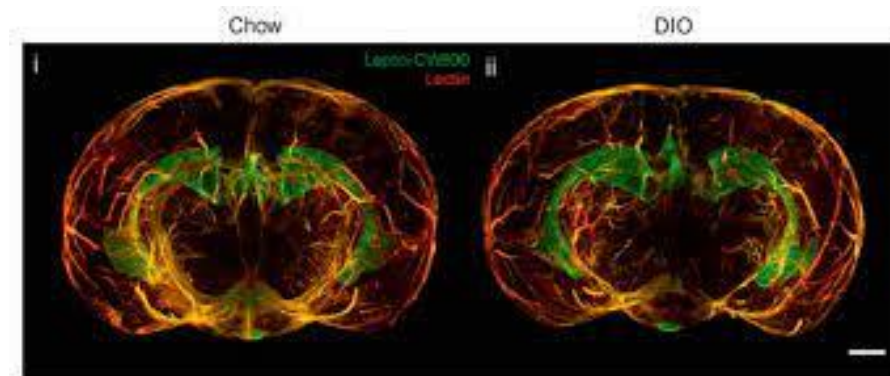


Leptin as the Major Signal for Adaptation to Starvation?

- Leptin receptors in many peripheral tissues and brain regions
 - Somatic: reproduction, liver and enteric metabolism, hematopoiesis, and immunity
 - Psychological/behavioral effects
- Starvation induces somatic and mental changes
 - Leptin-mediated effects via neuroendocrine axes
 - Direct effects of leptin on peripheral and central tissues
 - Graded response to starvation via circulating leptin?

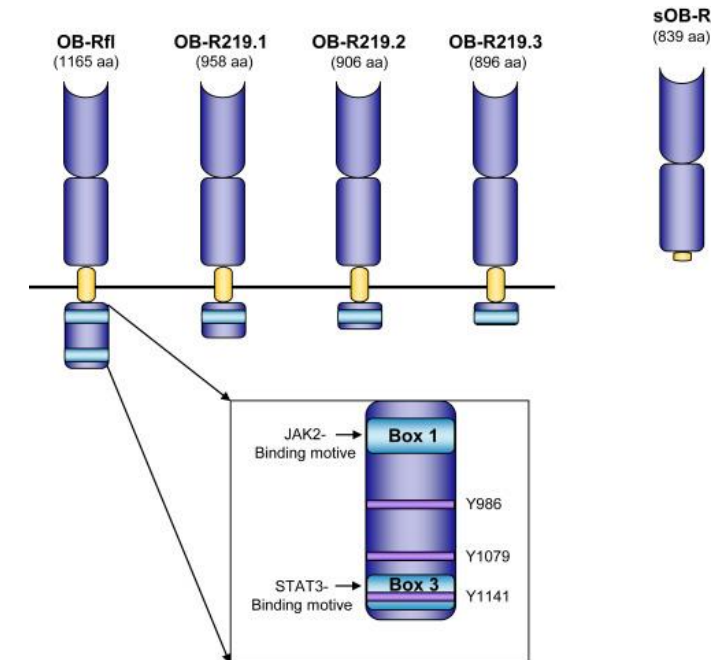


Liu et al Developmental Cell 2022



Harrison et al., Int J Obes 2019

Hebebrand et al., Frontiers in Psychology 2019, Neurosci Biobehav Reviews 2022, Nat Endocrinol Rev 2023



Schaab and Kratzsch, 2015

Phenotype of the *ob/ob* Mouse

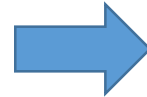
Starvation related symptoms:

hyperphagia
hypothermia
infertility
immune deficiency,
insulin resistance of starvation
euthyroid sick state
depression
reduced physical activity
impaired sleep
reduced brain weight
constipation

Red: not observed in restricting AN

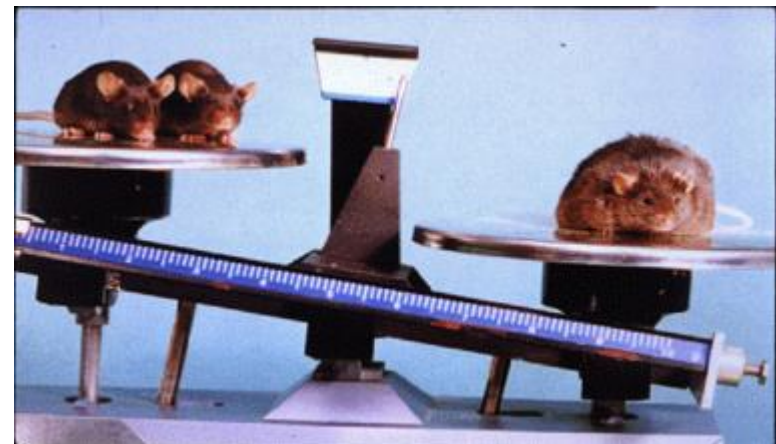
low leptin level: dangerously low adipose tissue mass

coexistence of obesity and starvation-induced symptomatology

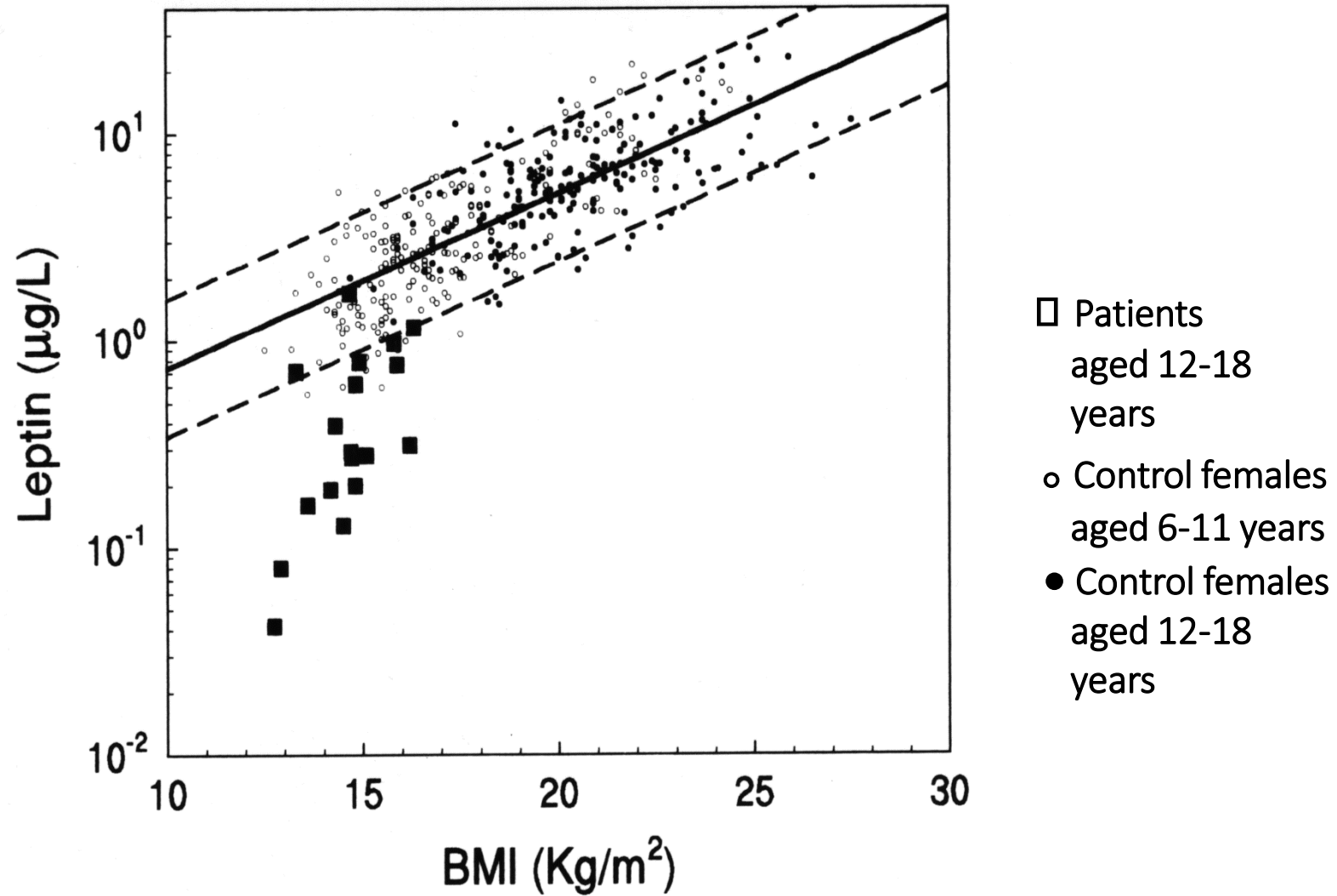


leptin treatment corrects ALL abnormalities: wide-sweeping effects of the adaptation to starvation triggered by this hormone

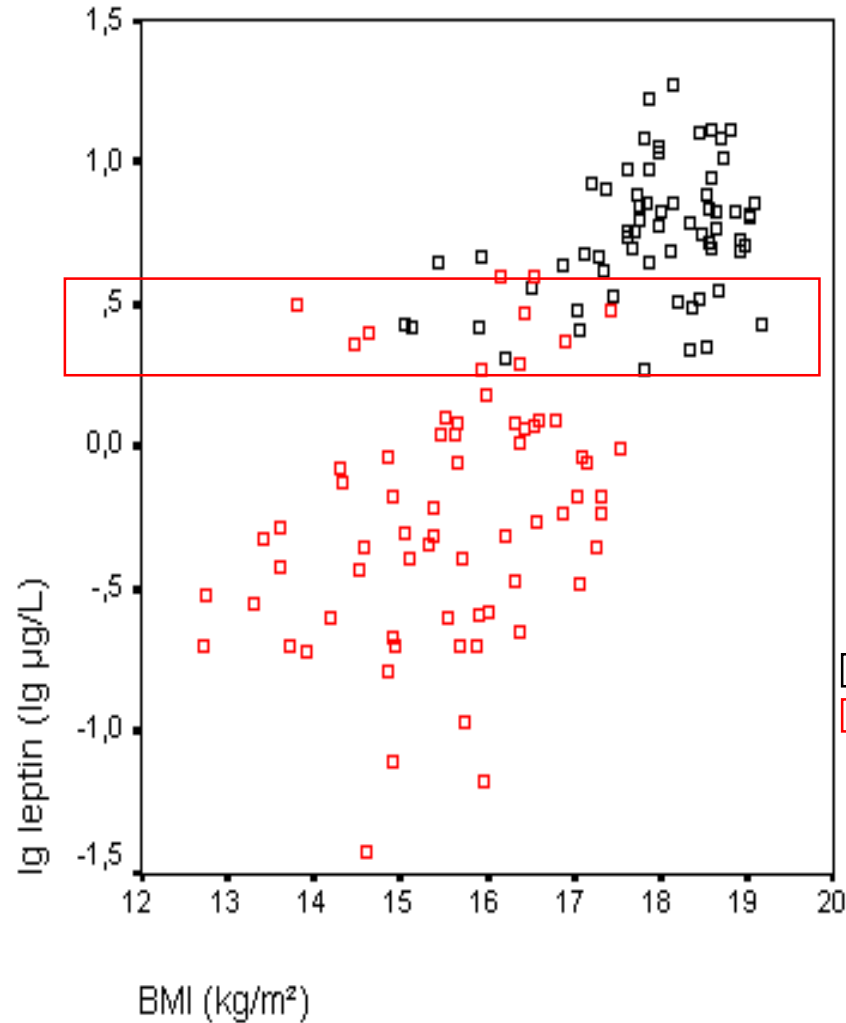
Leptin as 'master switch'



Serum Ig10 Leptin Levels in Acute Anorexia Nervosa



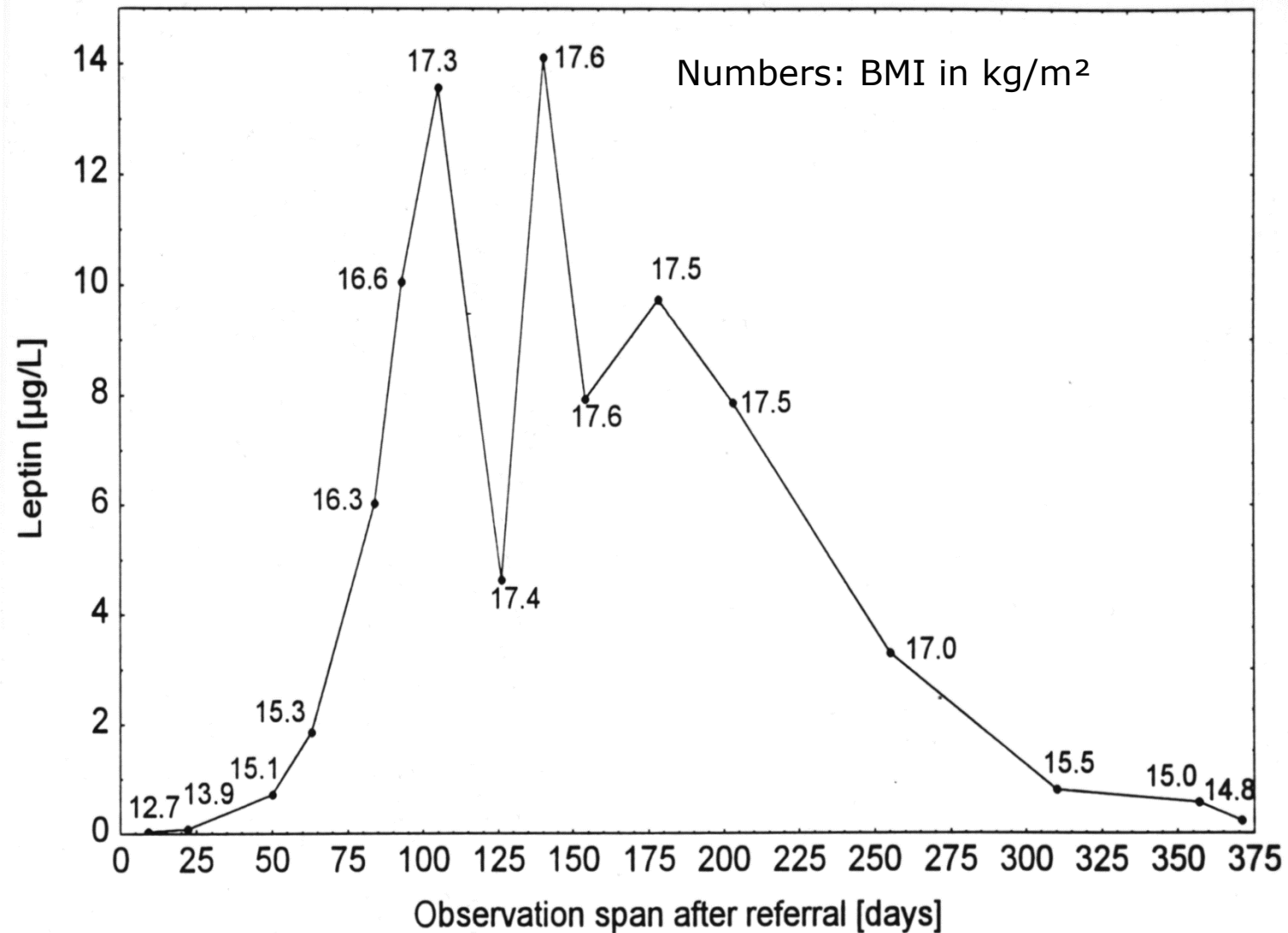
Leptin in AN Patients and Healthy Underweight Controls



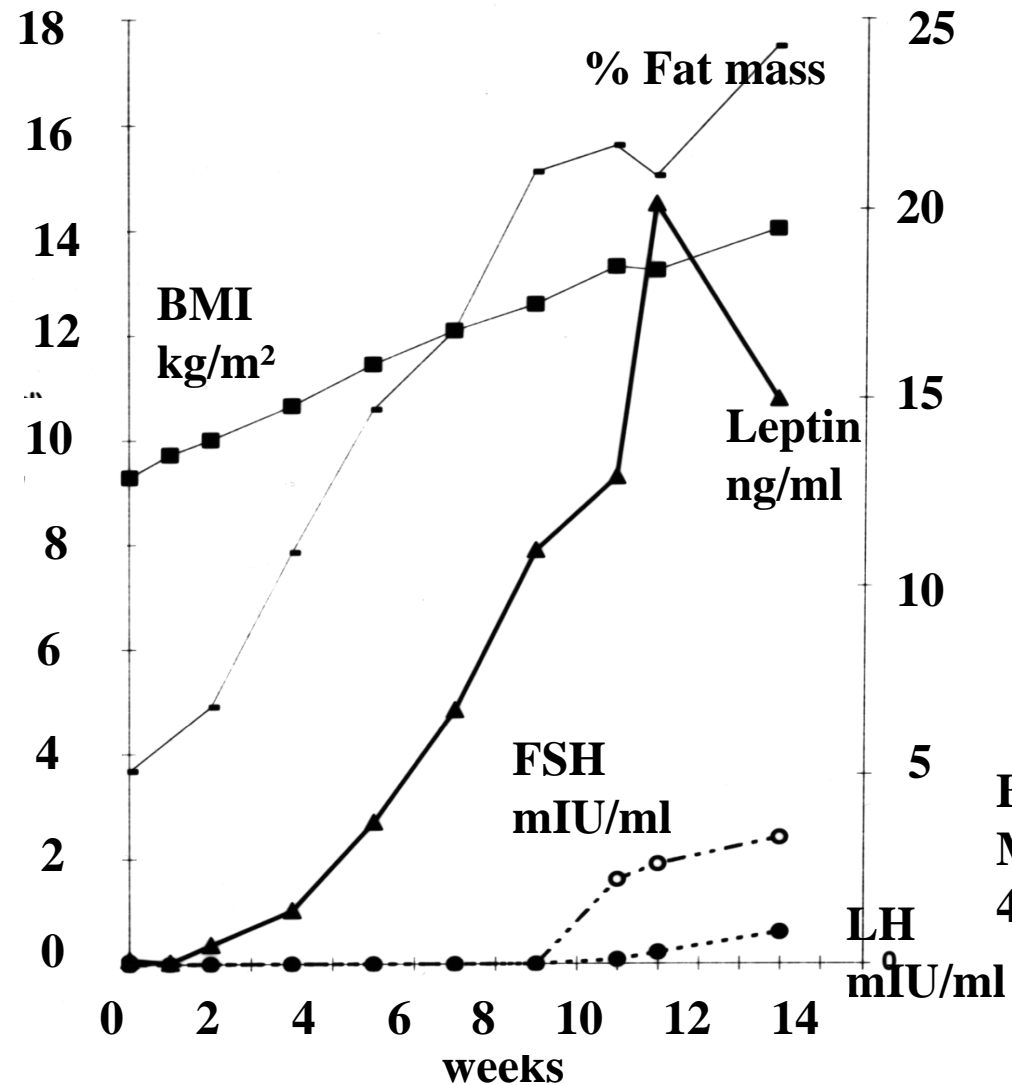
Borderline range: 2-4ng/ml

□ Controls
□ Patients

BMI and Serum Leptin Levels during Weight Recovery and Subsequent Relapse within a One Year Period



Serum Leptin and Gonadotropin Levels during Weight Gain



Ballauff et al.,
Mol Psychiatry
4:71-75; 1999

Hypothalamic Amenorrhea: Treatment with Human Recombinant Leptin (Metreleptin)

- 8 females with hypothalamic amenorrhea of ≥ 6 months duration (mean: 5 years)
- 6 untreated controls
- Metreleptin (r-metHuLeptin) for three months
 - Increment of serum LH levels within 2 weeks
 - Increments of maximal follicle diameter, size of ovary and serum estrogen level within 3 months
 - 3 patients ovulated, 2 pre-ovulatory follicles
 - No significant weight loss; no side effects except reduction of appetite in third month of treatment

Semi-Starvation Induced Hyperactivity

Anorexia Based Hyperactivity

Restriction of food intake (1 h/d) and unlimited access to running wheel

**Food intake declines strikingly,
running wheel activity increases**

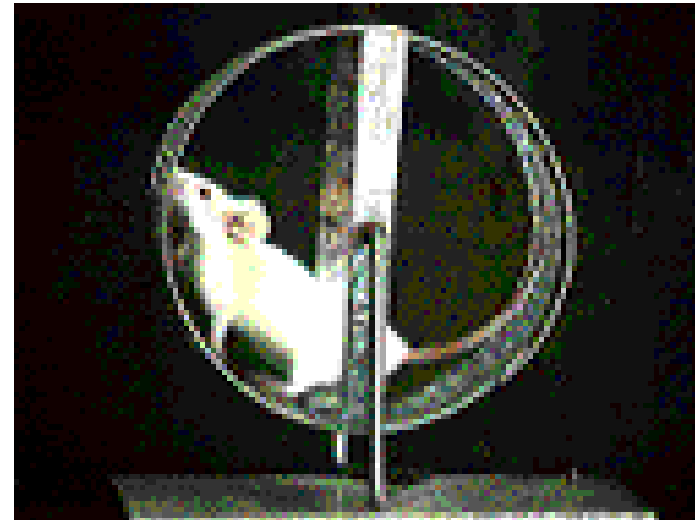
Food-anticipatory activity

**Only model for non-human mammals
choosing self-starvation over
homeostatic balance**

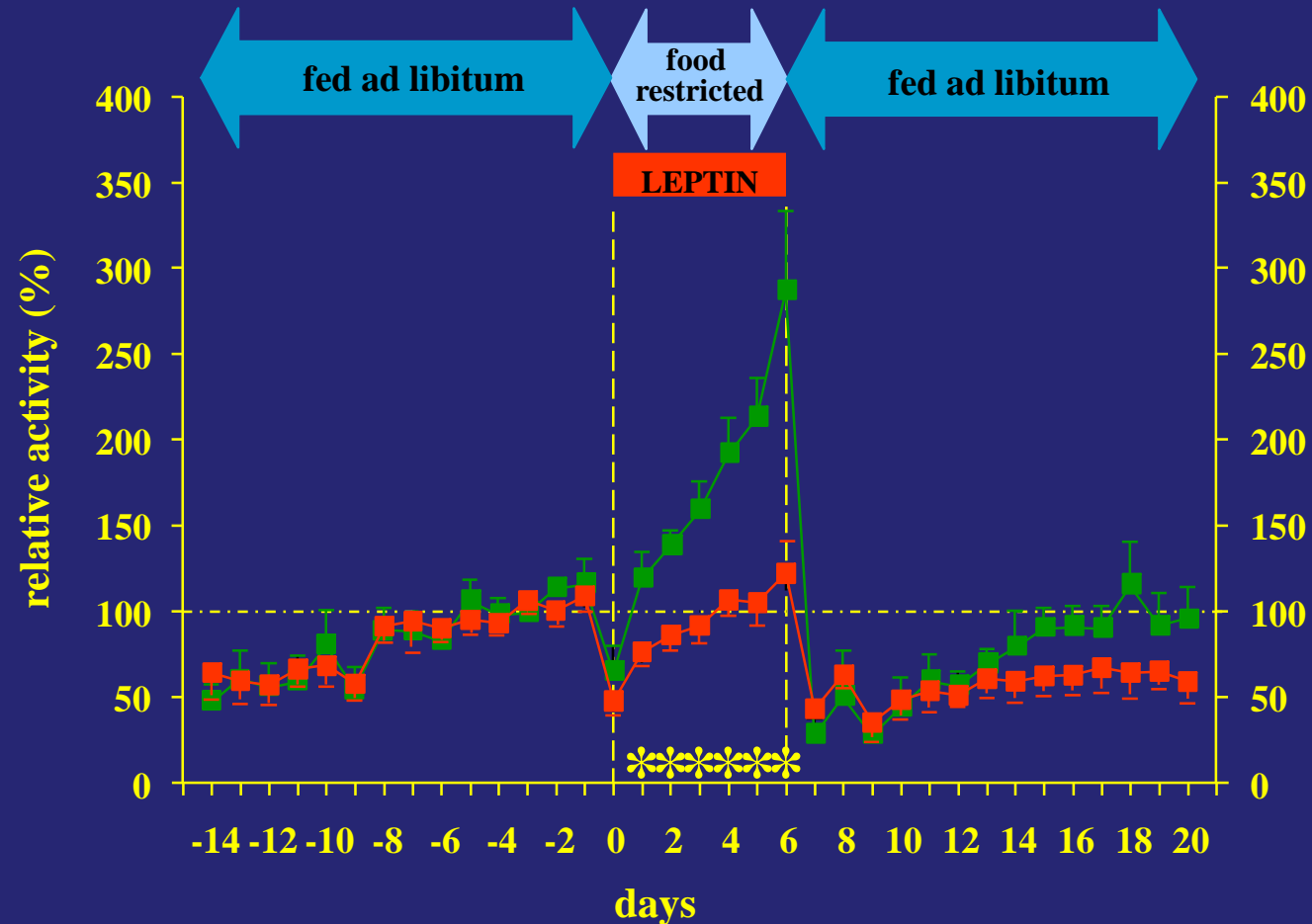
Stronger in female and young rats

Early life stressors increase susceptibility
Cold temperature, early weaning

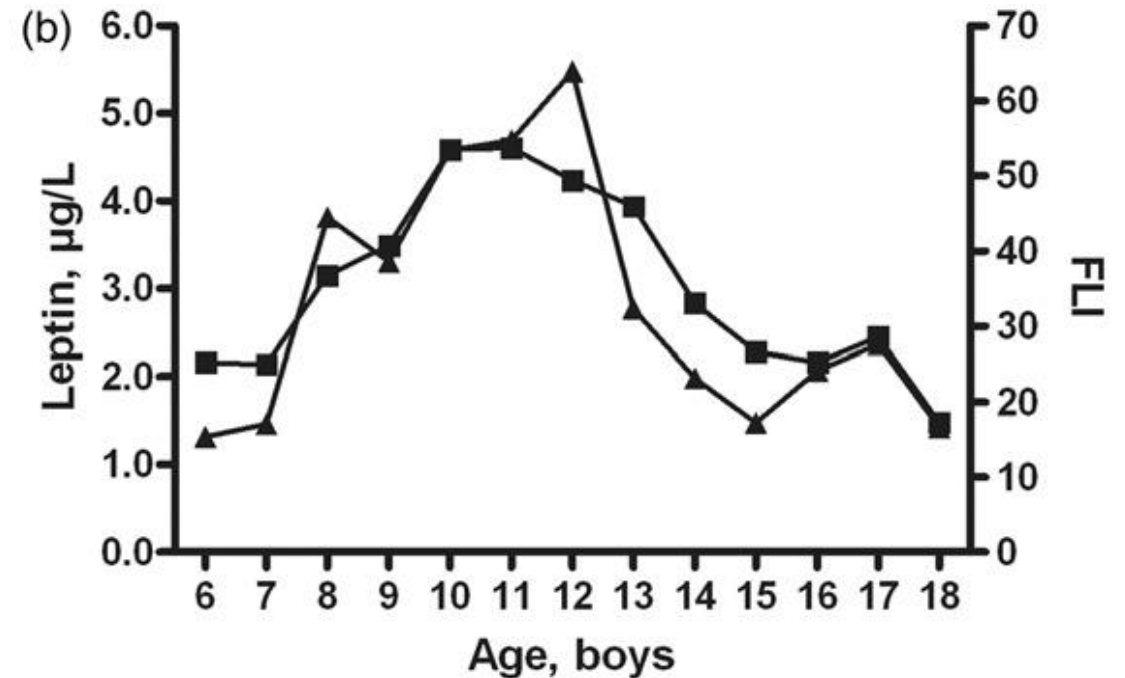
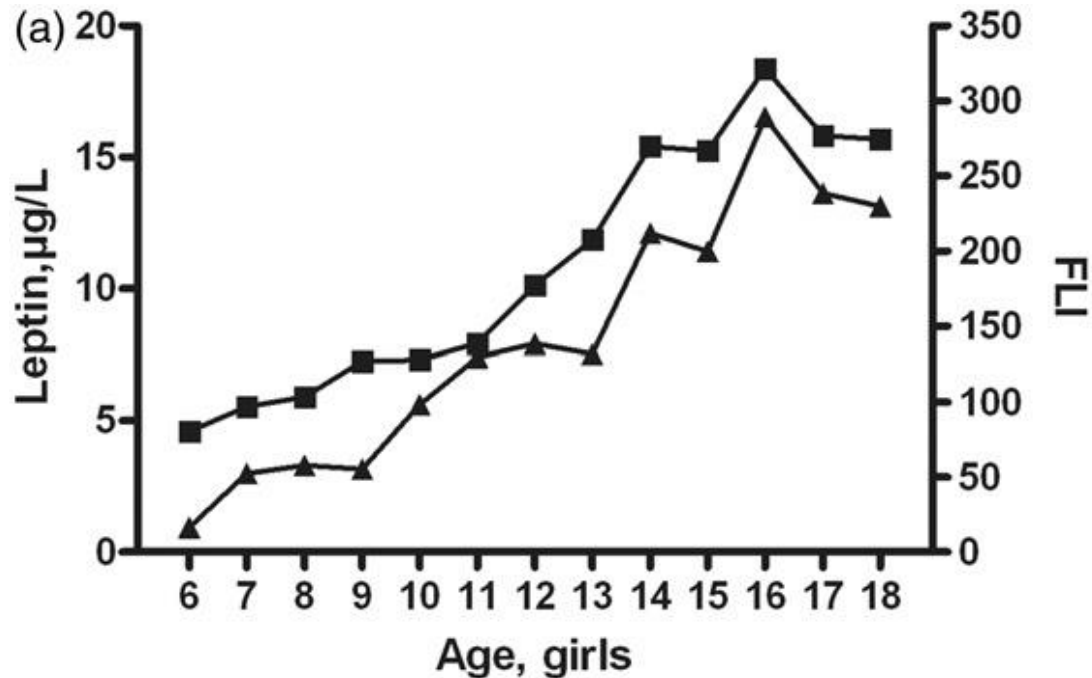
Amelioration by enriched environment



Leptin Suppresses Semi-Starvation Induced Hyperactivity

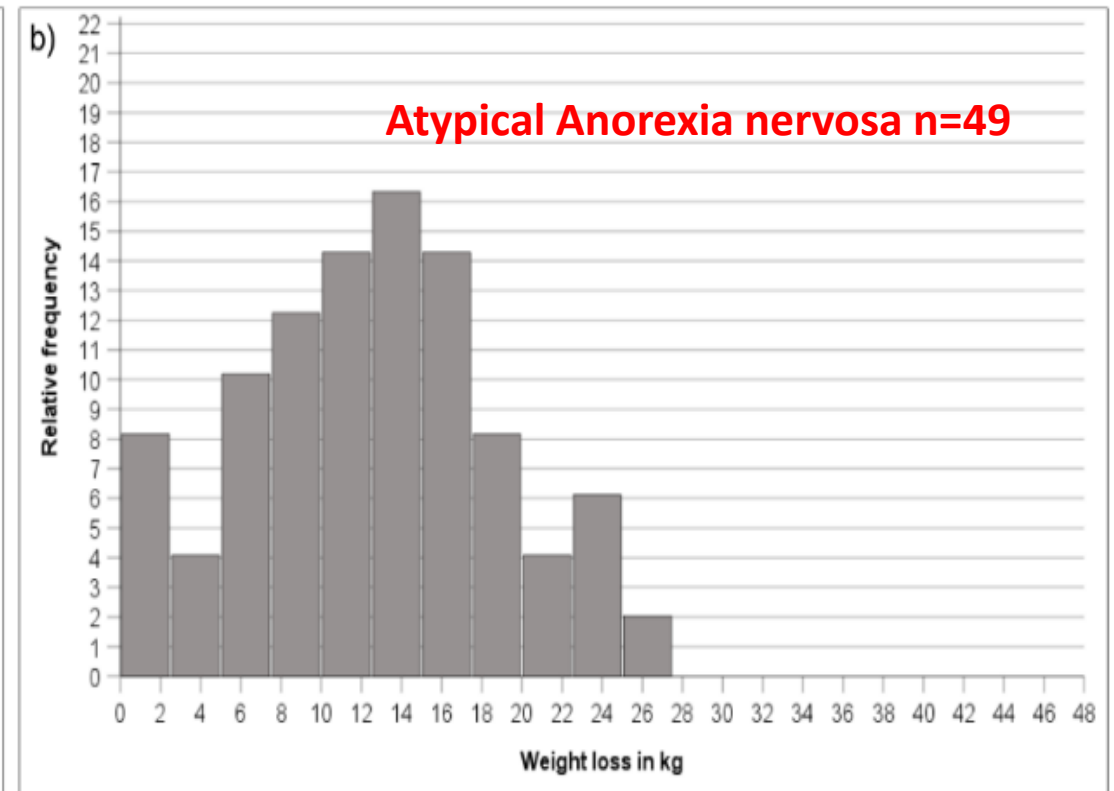
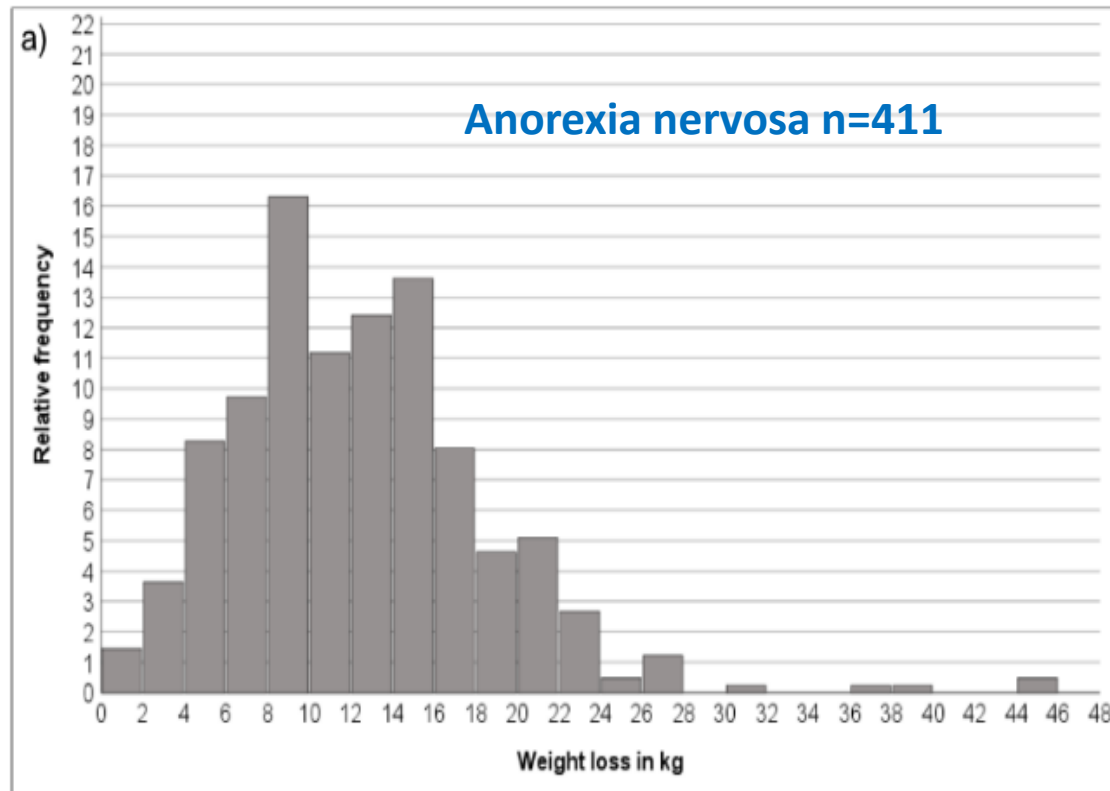


Sex Differences in Leptin Secretion During Puberty

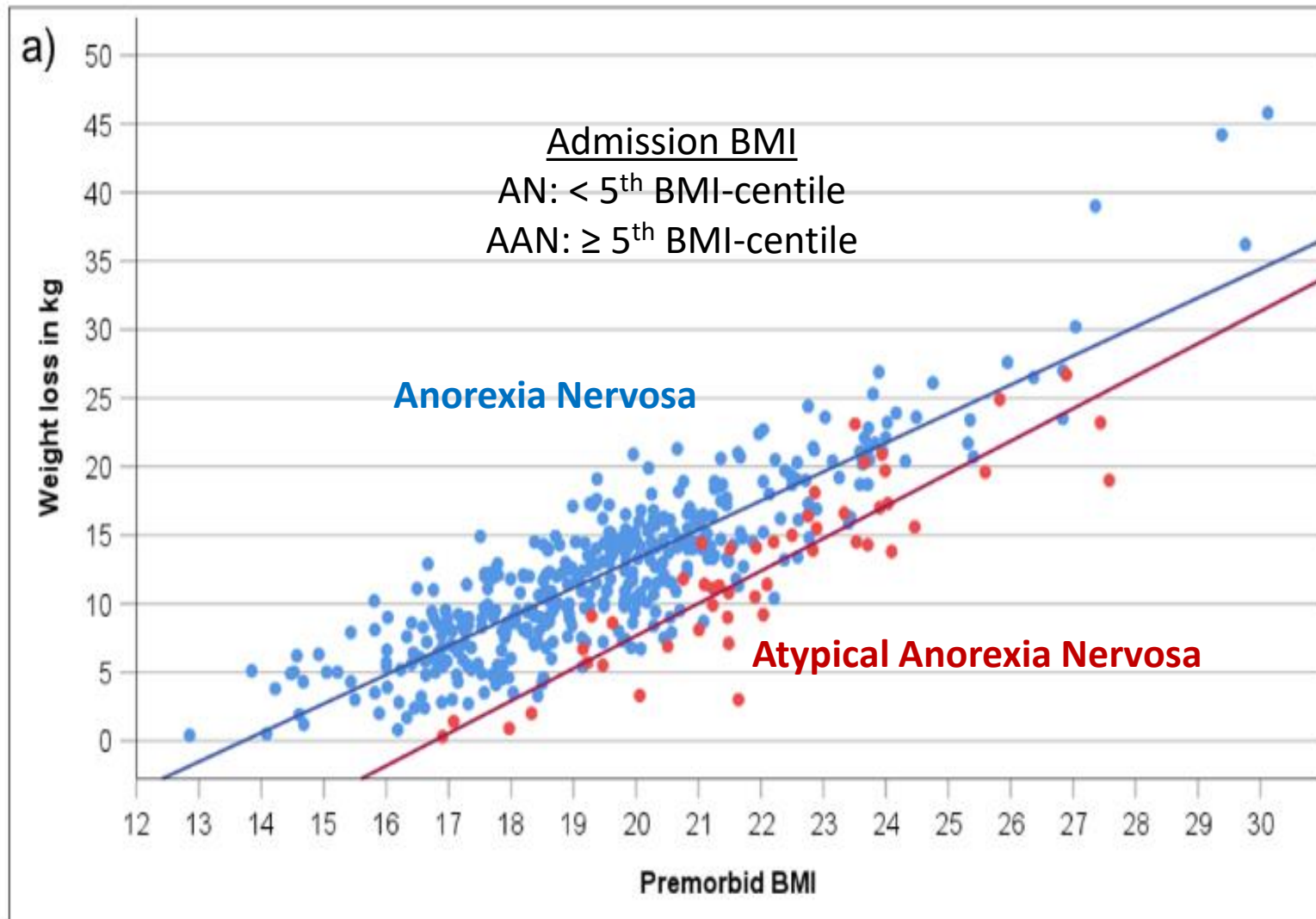


- Leptin
- ▲ Free Leptin Index

Weight Loss Distributions in Female Adolescents with Anorexia Nervosa



Relationship between Premorbid BMI and Weight Loss in Kg



Non-parametric
Spearman
correlations

AN: $\rho = 0.84$

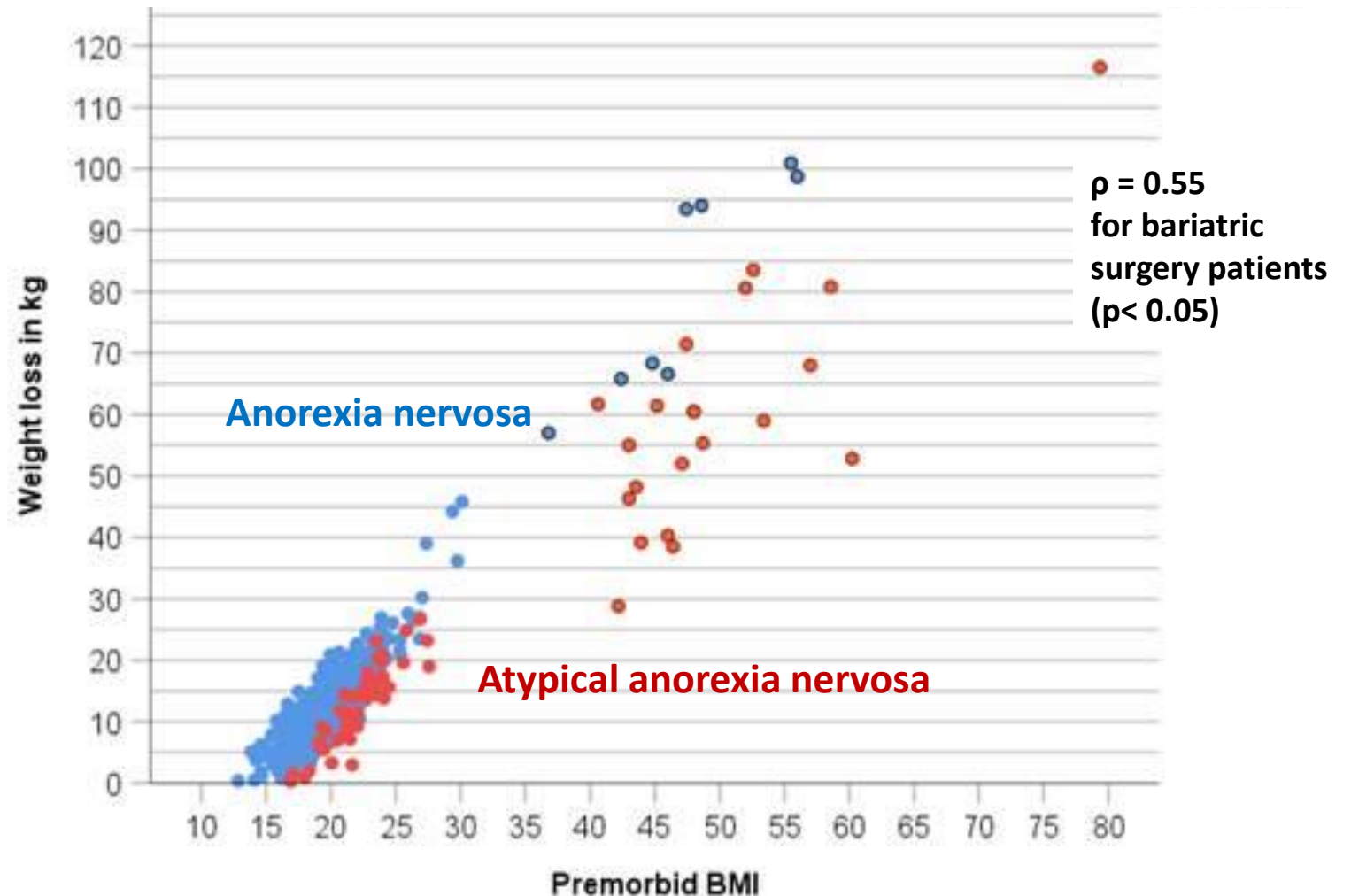
AAN: $\rho = 0.89$

Premorbid BMI estimated from recalled weight prior to onset of weight loss and measured height at admission

Hebebrand et al.,
Int J Eat Dis, in press

Relationship between Premorbid BMI and Weight Loss in Kg

- 460 patients with AN
BMI < 5th centile
 - 49 patients with **AAN**
BMI ≥ 5th centile
 - 29 patients with an AN-like phenotype after bariatric surgery
- AN:** BMI < 18.5 kg/m²
AAN: BMI ≥ 18.5 kg/m²

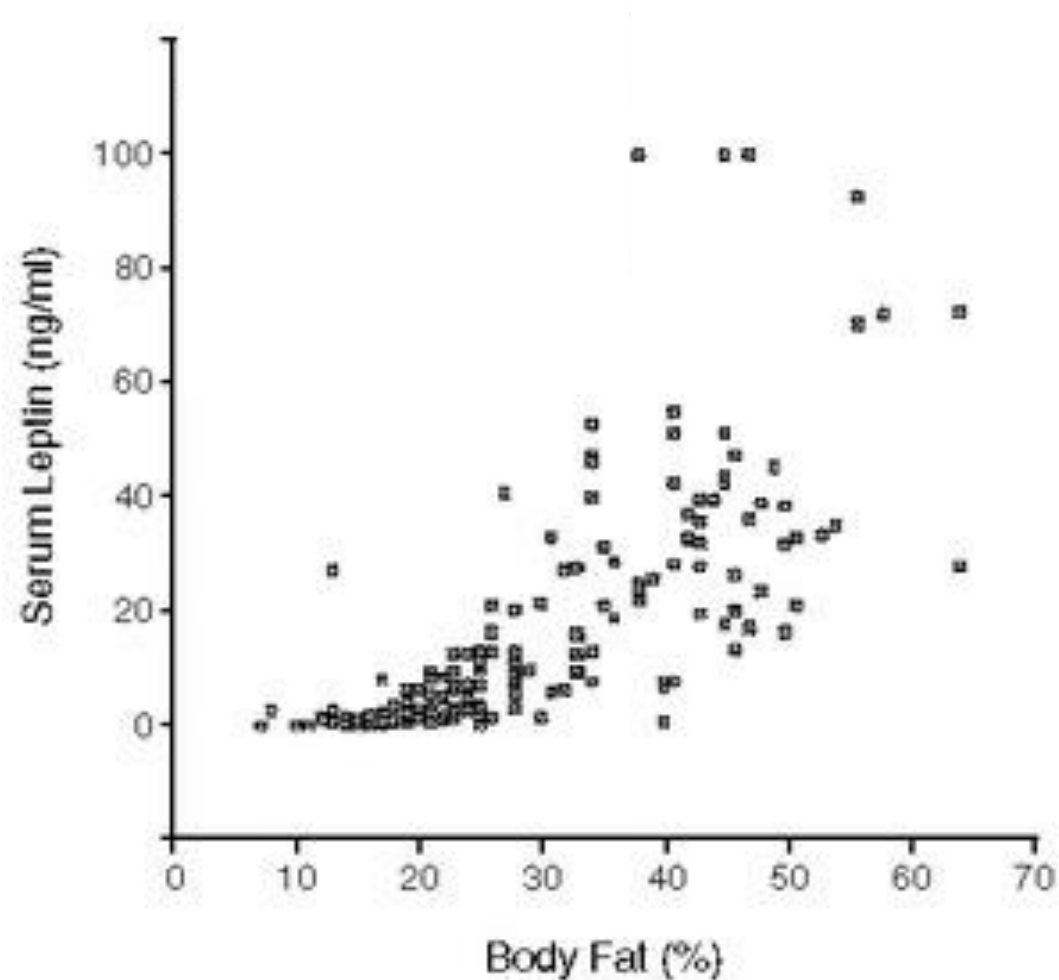


Relationship between Serum Leptin Levels and Percent Body Fat

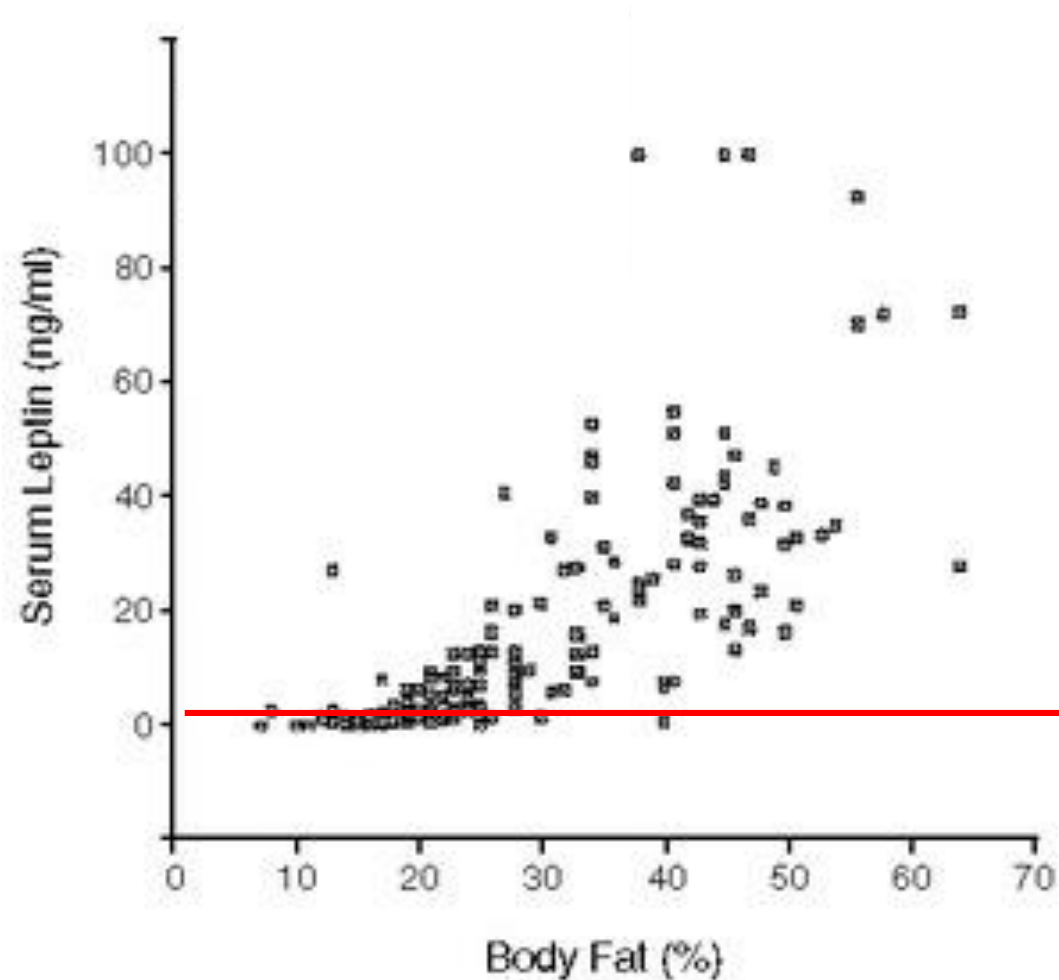
Females and Males

136 normal weight probands

139 probands with obesity

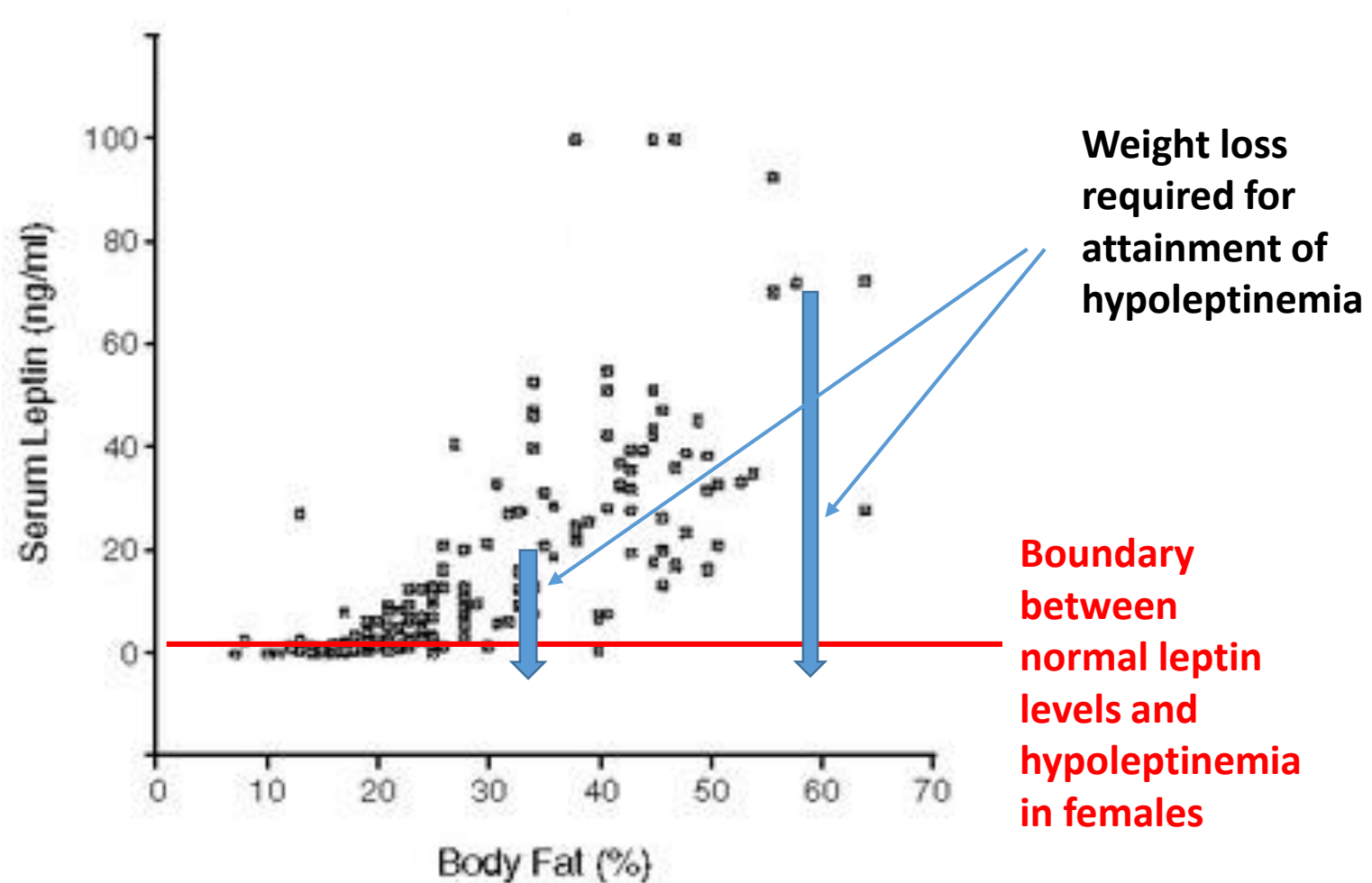


Relationship between Serum Leptin Levels and Percent Body Fat



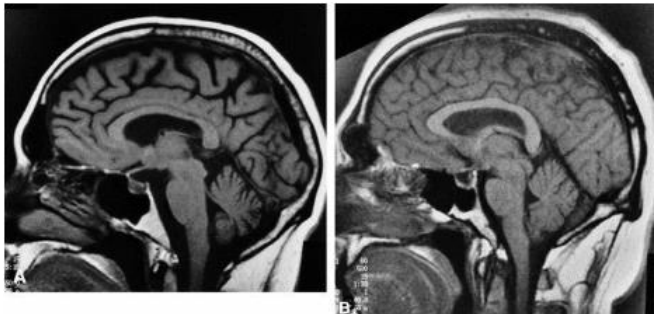
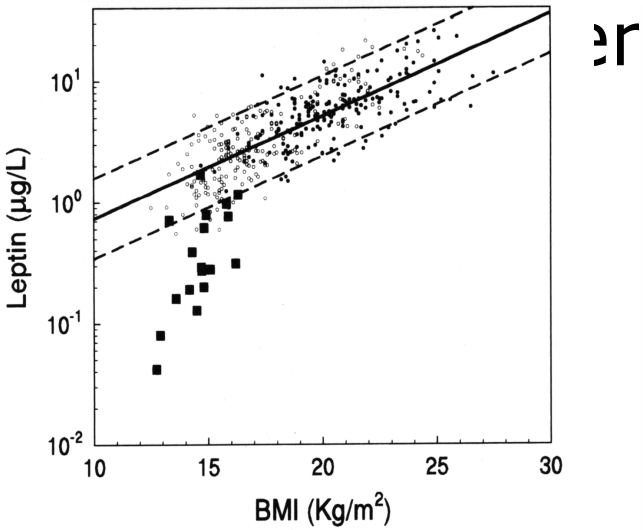
Boundary between normal leptin levels and hypoleptinemia in females: 2 ng/ml

Relationship between Serum Leptin Levels and Percent Body Fat



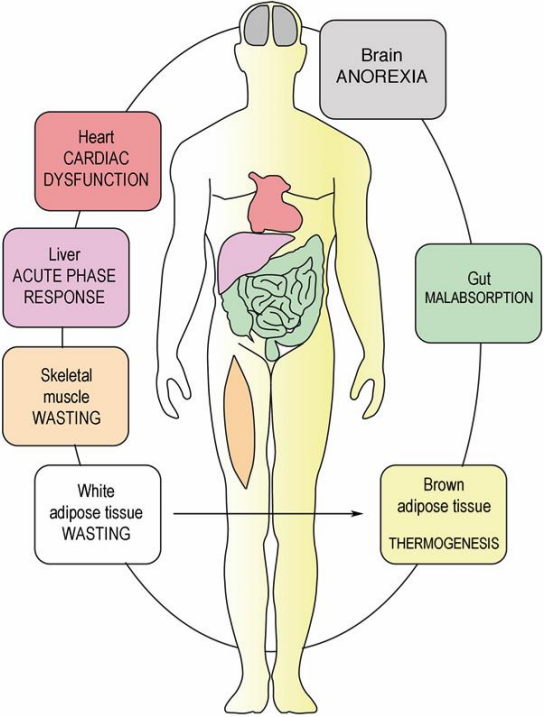
HYPOTHESIS >> LEPTIN IS THE KEY

Hypoleptinemia in patients with anorexia nervosa



Patient

Control



Hypoleptinemia triggers adaptation to starvation

Main Symptoms

SOMATIC

PSYCHOLOGICAL

- AMENORRHEA
- HAIR LOSS
- REDUCED TEMPERATURE
- BRADYCARDIA
- HYPOTONIA

- TIREDNESS
- FATIGUE
- INSOMNIA
- INNER TENSION
- RIGIDITY
- CONCENTRATION
- SPONTANEITY



Treatment of Anorexia Nervosa with Leptin

■ Chiesi Farmaceutici:

- Portfolio of drugs for patients with orphan diseases

- Metreleptin approvals

- FDA (2014; Myalept®): generalized lipodystrophy (GL) and congenital leptin deficiency
- EMA (2018; Myalepta®): GL and treatment resistant partial lipodystrophy



Off-label Metreleptin Case Studies of Patients with Anorexia Nervosa

- > 40 patients (2 males; 7 published cases) treated in 10 hospitals
- Standard treatment: eating plan; psychotherapy, co-medication on individual basis
- Inclusion criteria for off-label metreleptin
 - Severe AN, Atypical AN
 - Written informed consent (patients/parents)
- Dosing dependent on clinical observations
 - Dosing periods mostly between 6 and 24 d
 - 1 patient 80 d, 1 patient with comorbid partial lipodystrophy 5 months
 - Dosages between 3 and 12 mg/d

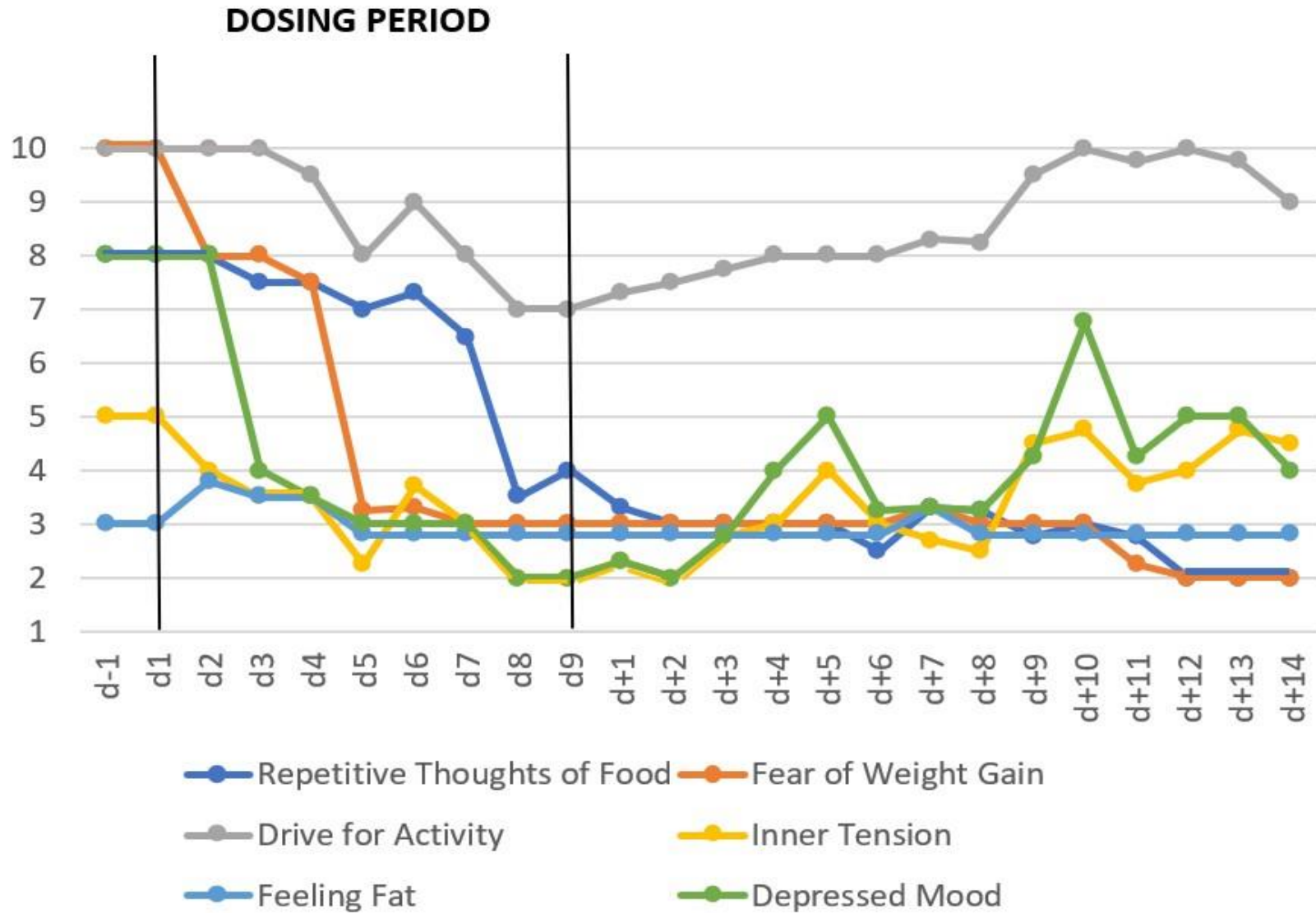
Improvements Noticeable Within 1-5 Days



IMPROVED SLEEP
IMPROVED MOOD
REDUCED INNER TENSION
REDUCED URGE TO MOVE **REDUCED**
IMPROVED SOCIAL INTERACTION
REDUCED PREOCCUPATION WITH FOOD
REDUCED WEIGHT PHOBIA
IMPROVED CONCENTRATION AND MEMORY
INCREASED APPETITE UND HUNGER
CONSTIPATION RELIEF
IMPROVED SKIN TURGOR
IMPROVED WOUND HEALING
INCREASED LEUCOCYTE COUNT

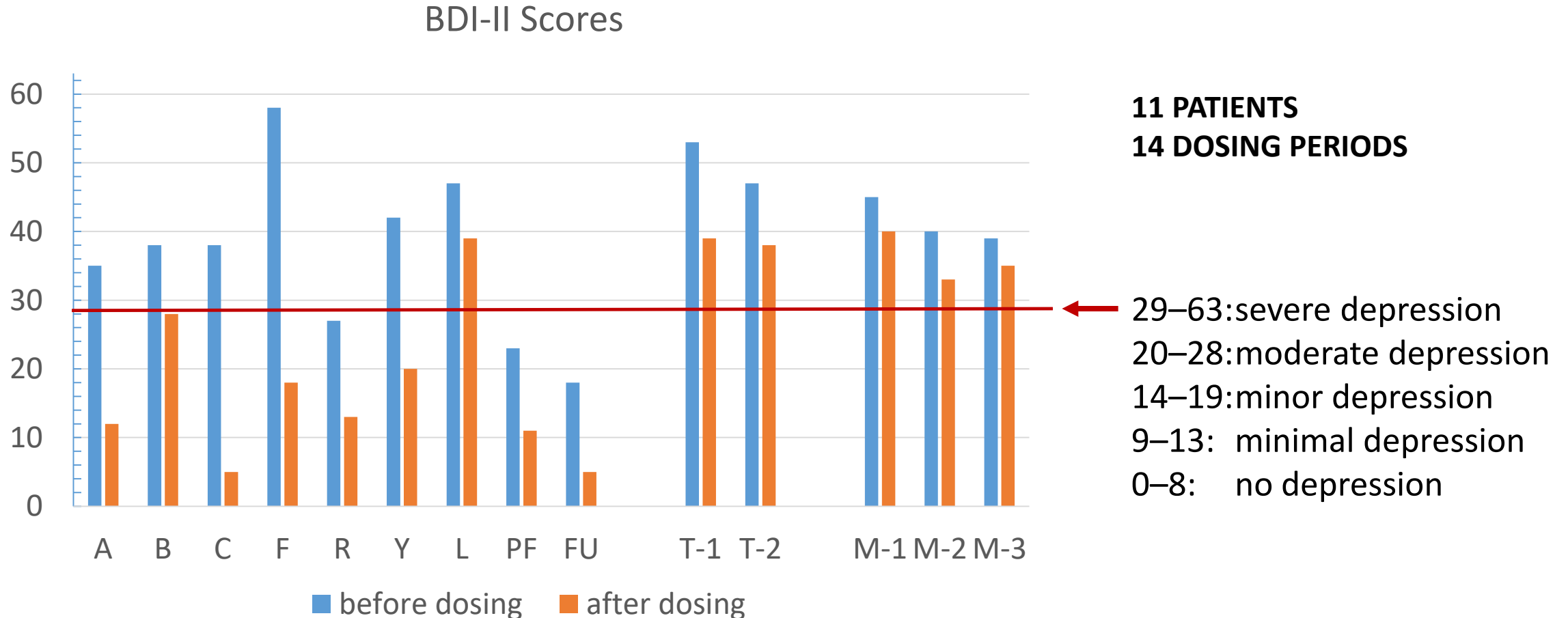
Visual Analog Scales: Self-Rated Key Cognitions and Emotions

PATIENT A



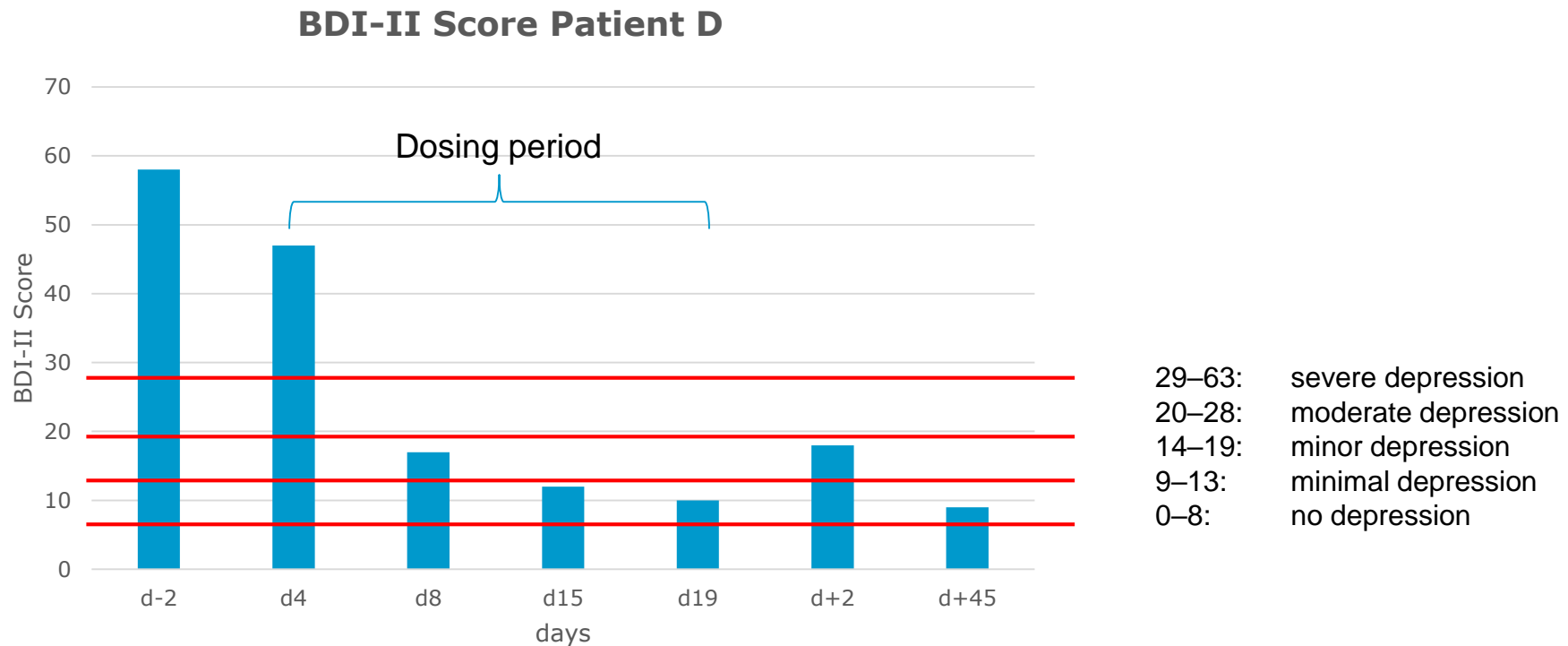
VAS (1-10) filled in 2-3 X/d
Means for items

PATIENT SELF-RATINGS FOR DEPRESSION



National Institute for Health and Care Excellence (NICE) suggest difference of ≥ 3 BDI-II points is a clinically significant treatment effect for normal depression (mental health guidelines developed by the National Collaborating Centre for Mental Health, 2004)

Self-Ranked Depressive Symptoms in Patient F up to 45 Days after End of Dosing Period



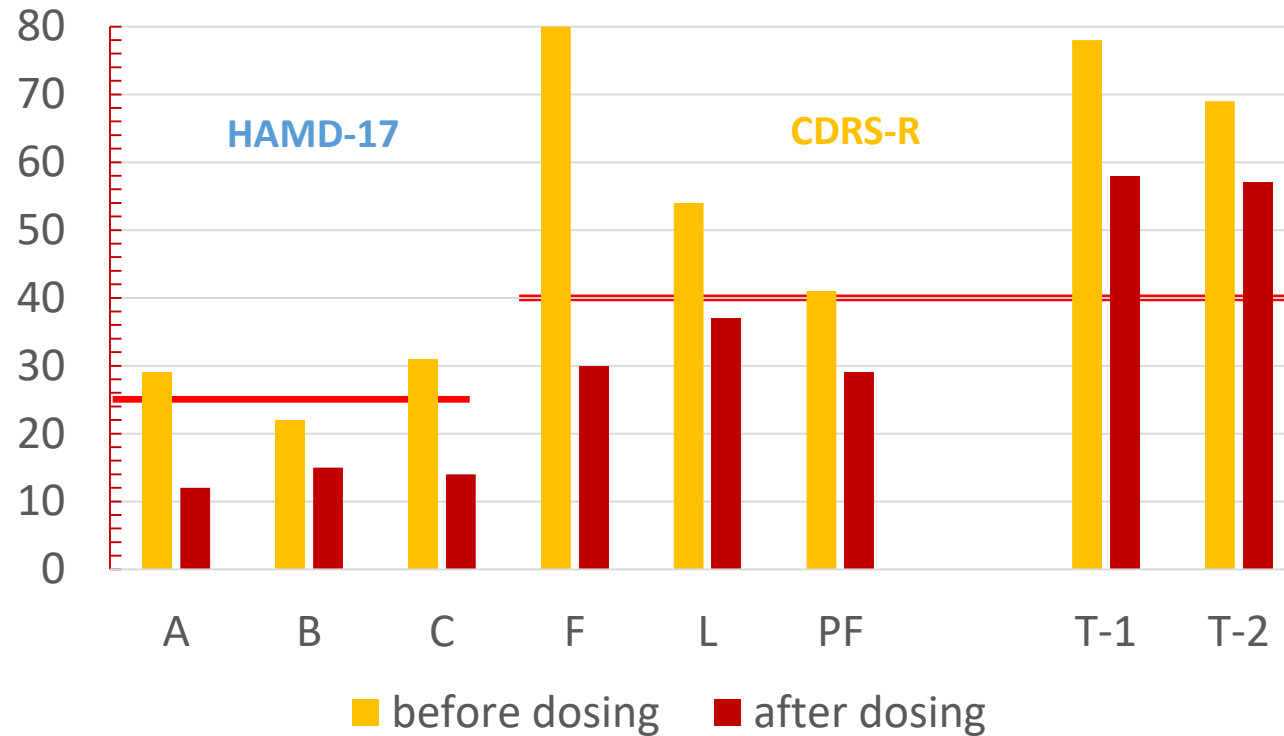
BDI-II: Beck & Steer 1987

EXPERT (CLINICIAN) RATINGS

HAMD-17 scores

- ≥ 25: severe depression
- 17–24: moderate depression
- 9–16: minor depression
- 9–13: minimal depression
- 0–8: no depression

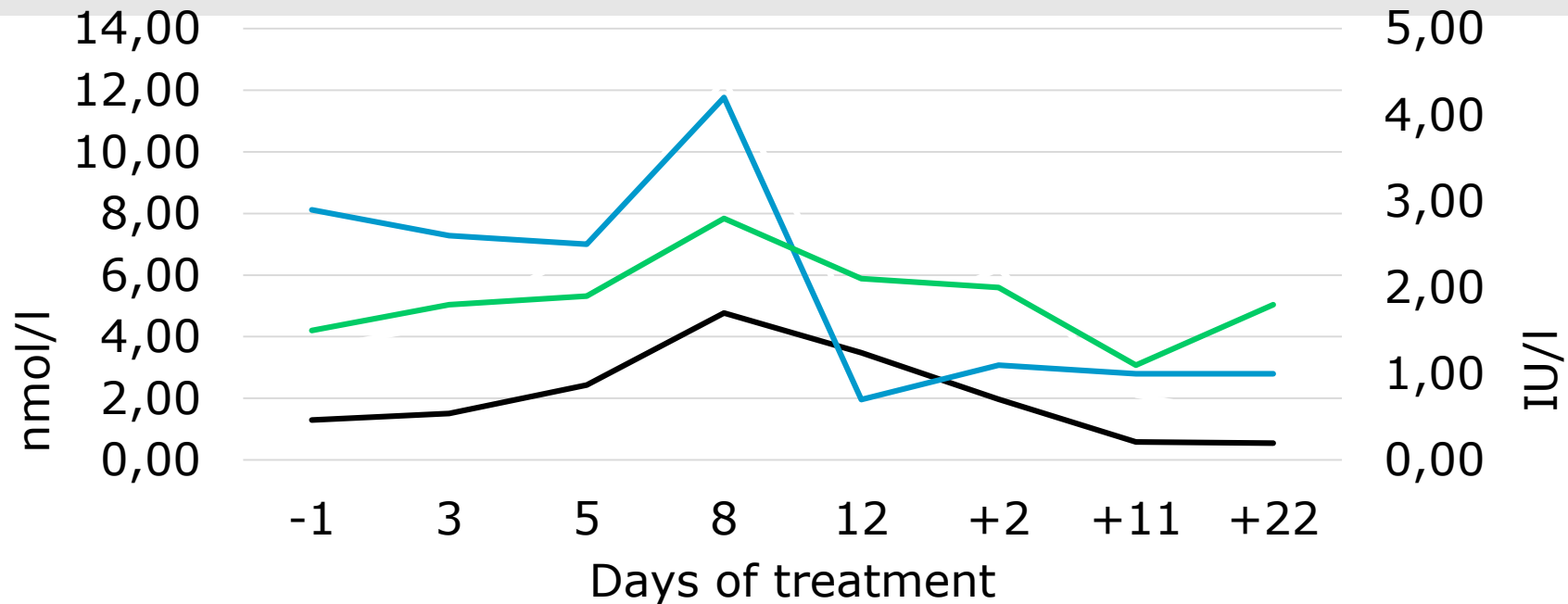
Clinician rated HAMD-17 (adults) or
CDRS-R raw score (adolescents)



**11 PATIENTS
7 TIMES RATED
BY HAMD OR CDRS-R**

CDRS-R scores
≥40 depression
≤28 remission

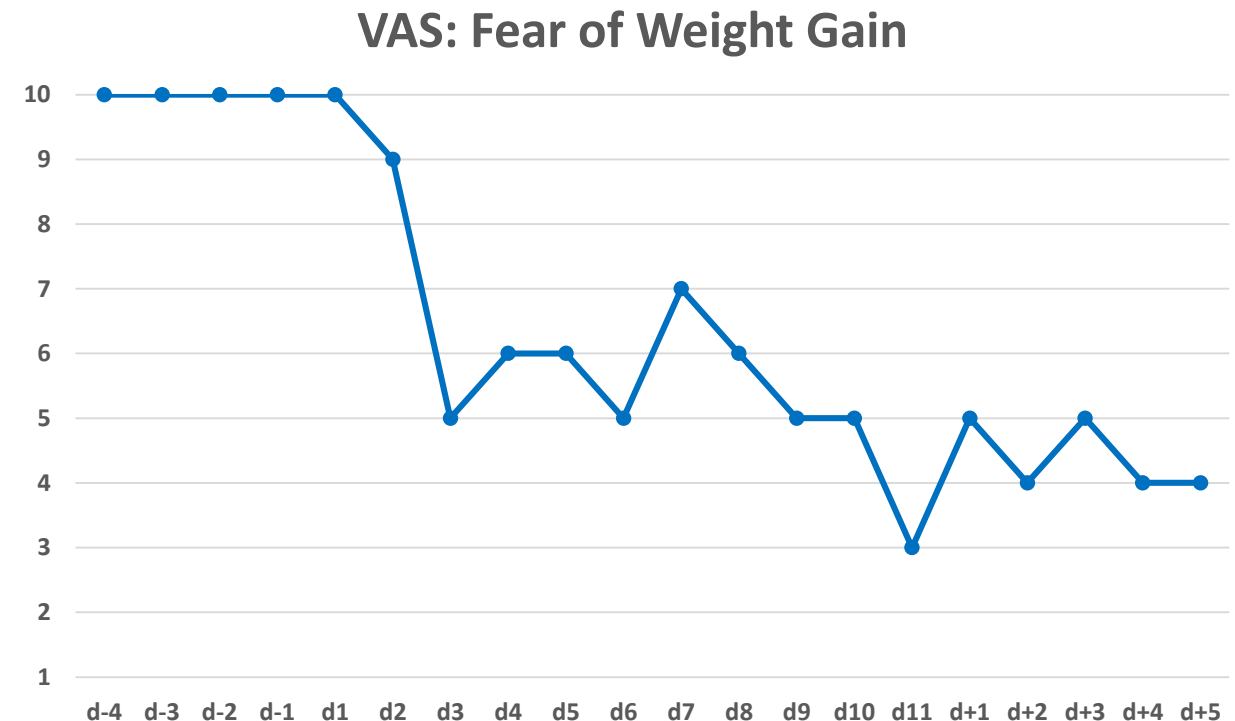
Increased Serum Levels of FSH, LH and Testosterone During Metreleptin Dosing in Male Patient F



- Testosterone (nmol/l)
- bioavailable Testosterone (nmol/l)
- LH (IU/l)
- FSH (IU/l)

Metreleptin and Atypical Anorexia Nervosa

- Weight loss of 21 kg (premorbid BMI: 27.12 kg/m²); admission BMI 20 kg/m²
- Serum leptin level: 2.4 ng/ml; upon adjustment for sex, BMI and Tanner stage between 1st und 5th centile
- 6mg/d metreleptin for 11 days
- BDI-II:
 - d-1: 29; d8: 12; d+10: 17
- EDI-2-Total score:
 - d-1: 95th centile
 - d10: 85th centile
 - d+10: 80th centile



Patient F: Parental Observations/Comments - Dosing Days 1 to 17

... stopped permanent crying, laughed for the first time for more than six weeks ...

... became clear in his thoughts and expressions, smiled a lot ...

... showed very good mood and made jokes ...

... allowed huggings and kept smiling ...

... reduced compulsivity (timing of running, showering) ...

... mentioned that his drive for activity was reduced ...

... open for topics other than ED related for the first time in a long time...

... his former personality is re-appearing ...

Maternal account: Patient R

- Severe AN with fixations during prior inpatient treatment for feeding
- Metreleptin for 8 days, 7 X 6mg, 1 X 3mg
- Antidepressant effect noticeable to the patient as of dosing day 3
- Hunger increased during treatment, fullness decreased
- Subsequent daily phone contacts for 3-5 minutes for 3 weeks to reintroduce foods
- Weight gain of 20 kg (to 60 kg; 87th BMI centile)
 - premorbid overweight (\approx 85th BMI centile) and maternal obesity

R has made tremendous progress! 😊 Her **mood is usually positive** and she has lots of energy. She can attend school without any problems, because she eats an extended breakfast at seven. For long school days she takes care to bring ample food supplies to school, which she can eat in the presence of her peers. When she comes home, she is **HUNGRY** ! Even when I cannot accompany her at meals, she manages to prepare and eat her food herself. She really does an excellent job! I have now allowed her to participate in gymnastics and judo lessons, because she has intermittently reached her premorbid body weight.

I am so happy that you enabled her to open up this damned cage door. Several people have noticed that R is **much more content and open for contacts**.

The Barren Room (Patient T; AN, OCD, PTSD)

A new method came to get me through the window. For the first time after such a long time, I looked out between the gaps of the shutters. I saw life, friends and future, but somehow, I didn't care. I saw people trying to help me, but something stopped me. At some point I managed to open the shutters completely, I was overwhelmed and shocked at the same time. I saw what was outside the room again after such, such a long time. I saw life as I knew it from before, but I also lived in my room, I was torn. Which of these is the real life?

More and more I discovered and observed life outside, I began to like it, I wanted this life, too.

Getting out of this room was my greatest wish, but the door and the window were both closed.

The life outside encouraged me, I managed to get up from the concrete floor, I went to the window, the window openers were locked. It took me some time to find an idea I could try to open the window. I took a piece of broken concrete, no matter how heavy it is, I carry it on with the motivation that I turn into strength, until I can finally break the windowpane with it, but it is not so easy, the concrete is heavy, the doubts are great and the room is my actual life that I am supposed to leave behind. But is it worth it? Why can't I just walk out the door and call it a day? Why does it come to so many difficulties?

DeepL Translate

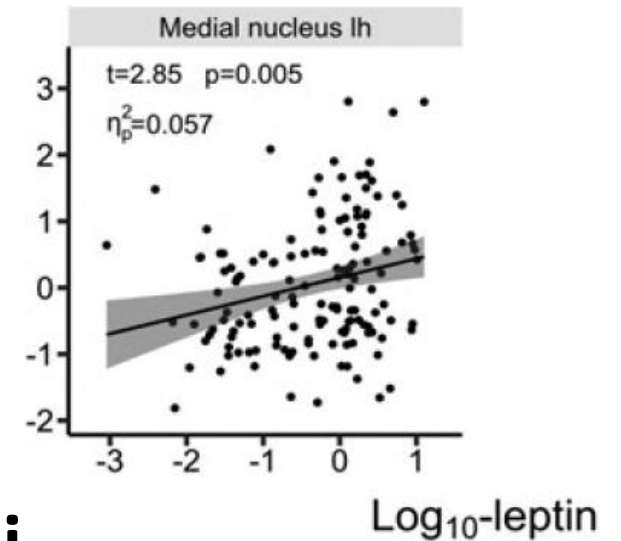


Placebo Effects?

- **No medication licensed for AN; no evidence for strong placebo effects in RCTs**
- **Hypothesis driven approach**
- **Homogeneous improvements: reduced preoccupation with food, improved mood, increased concentration and social contacts**
- **Observed improvements partially not covered in informed consent**
- **Somatic and mental improvements consistent with current knowledge of effects of leptin**
- **Evidence for mood improvement in patients with congenital leptin deficiency and lipodystrophy treated with metreleptin**

Leptin and Volumes of Amygdala Nuclei

- Volumes of most nuclei reduced in acutely ill patients
- 4 nuclei with largest volume reductions upon adjustment for total volume of amygdala and of subcortical grey matter
- Rostral-medial nuclei positively associated with leptin levels (independent of BMI)
- Rumination (food, weight) associated with volumes of right accessory basal and cortical nuclei
 - Mediation of effect of leptin on weight related ruminations via these two nuclei
 - No relationship in healthy controls



Psychiatric Symptoms in Different Hormone Deficiencies

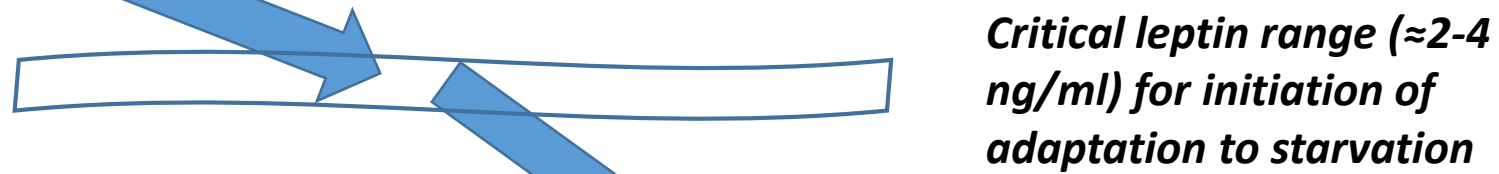
Hormone	Psychiatric Symptoms Upon Deficiency
Thyroid hormones	Fatigue, depression, hypersomnia, forgetfulness, inattention, mental slowness, emotional lability, reduced libido
Growth hormone	Fatigue, depression, anxiety, insomnia, reduced libido
Testosterone	<i>Males:</i> fatigue, depression, anxiety, reduced libido, anhedonia
Estradiol	<i>Females:</i> fatigue, depression, anxiety, insomnia
Cortisol	Fatigue, depression, reduced concentration, anhedonia

Progressive Loss of Fat Mass Progressive Decrease in Leptin Secretion

Premorbid body weight →

Step 1
Initial weight loss
Eating and physical activity under control

Step 2
Further weight loss
Reduced control of eating and physical activity
ENTRAPMENT



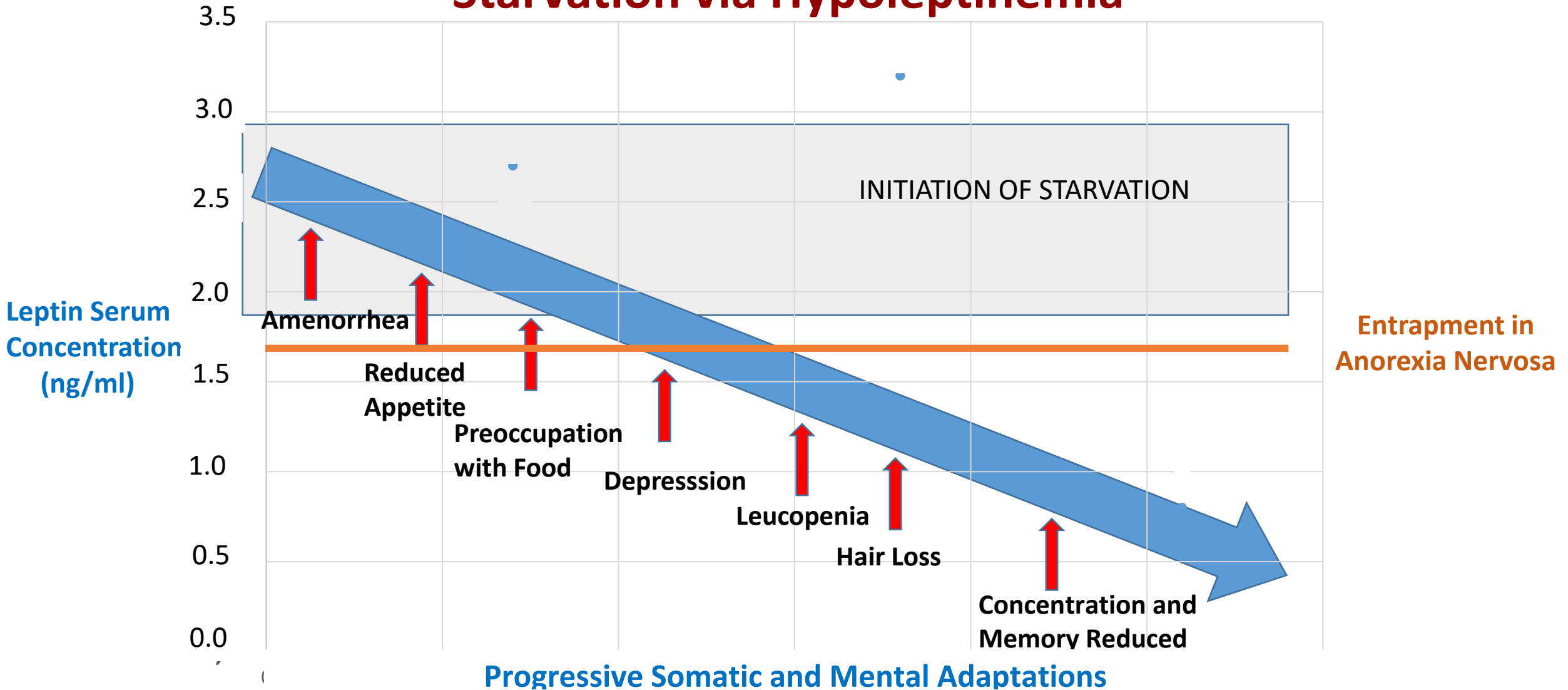
Normal leptin secretion
e.g. 10 ng/ml

Initial drop in leptin secretion
drop from 10 to 4 ng/ml

Absolute (or relative) hypoleptinemia
drop from 4 to < 0.1 ng/ml



Hypothetical Model Gradual Somatic and Psychological Adaptation to Starvation via Hypoleptinemia



Current Implications for Treatment

■ Psychoeducation:

- Psychological effects of starvation
- Little improvement during initial weight gain
- Weight gain represents means for purpose
 - Adipokines, leptin
 - Slow initial increase in serum leptin
- Provide feedback on improvements during weight gain
 - Formalized test battery to allow patient/caregivers to track changes over time

■ Relapse prevention

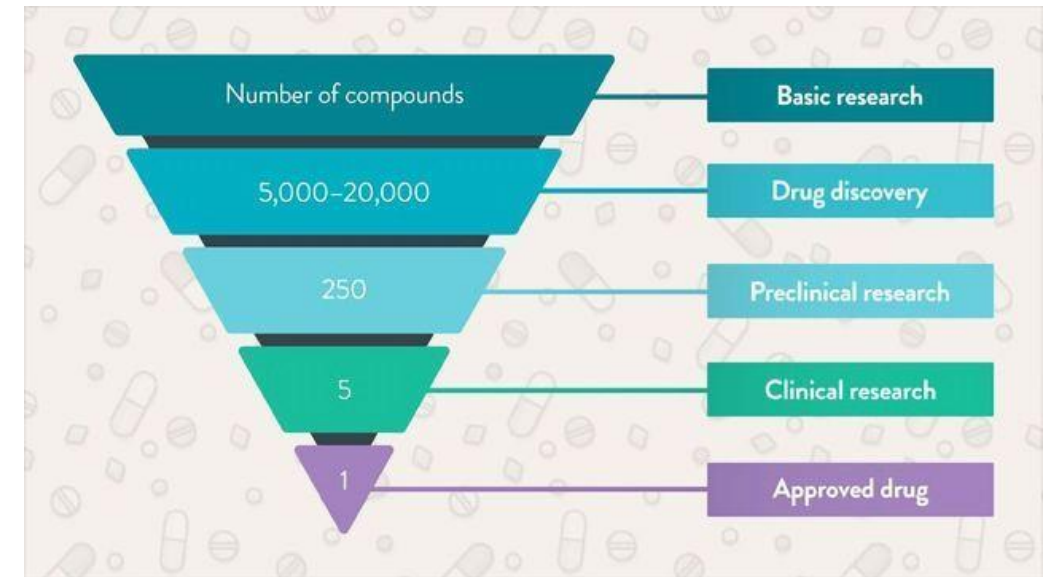
- Maintenance of a sufficiently high leptin level
 - Avoid leptin dips
 - Avoid intermittent reduction of caloric intake, stress

Loose Strings

- **Psychotherapy tailored to treatment with leptin analogs**
- **Atypical and typical Anorexia nervosa single disorder?**
- **Leptin - hormone with profound effects on psychological well-being?**
 - **Psychopharmacological effects of leptin only in starved humans?**
- **Duration of treatment, dosage?**
- **Mechanisms underlying response**
- **Sex dependent regulation of leptin with pronounced differences during puberty**
 - **Partial explanation for female predominance and manifestation age for eating (and affective) disorders?**
- **High price of metreleptin: treatment costs \approx 1300-2500 Euros/d**
- **Can „semi-starvation neurosis“ be treated with leptin analogs?**
- **Urgent need for RCTs and involvement of pharmaceutical industry**
 - **Support from experts, patient and parent groups**
 - **Independent case reports**

Problems Inherent to Development of Novel Drugs for Treatment of Anorexia Nervosa

- **Belief in psychogenic / psychodynamic etiology**
- **Limited neurobiological research**
- **Limited pipeline/portfolio of drugs**
- **Few solid hypotheses**
- **Dependence on chance findings**
- **Pharmaceutical industry: eating disorders are not a focus**
- **High costs for drug development up to approval**
 - **Current estimate: 1.1 – 1.6 billion \$**
 - **80-120 million \$ for repurposing**



Acknowledgements

- Gabriella Milos, Zurich
- Jochen Antel, Essen
- Martin Wabitsch, Ulm
- Susanne Tan, Essen
- Haiko Schlögl,
Michael Stumvoll, Leipzig
- Stephanie Fulton, Montreal
- Tom Hildebrandt, New York

- **Patients**
- **Parents**



Adult Weight Categories based on BMI (WHO, 1998)

Category	BMI (kg/m²)
Underweight	< 18.5
Normalweight	18.5 – 24.9
Overweight	≥ 25
Pre-obesity	25 – 29.9
Obesity Grade I	30 – 34.9
Grade II	35 – 39.9
Grade III	≥ 40

BMI Centiles for Females Aged 0 to 18 Years

Centile Cut-offs for Different Weight Categories/Disorders

Obesity: BMI \geq 97th centile

P97

Overweight: BMI \geq 90th centile

P90

P75

P50

P25

P10

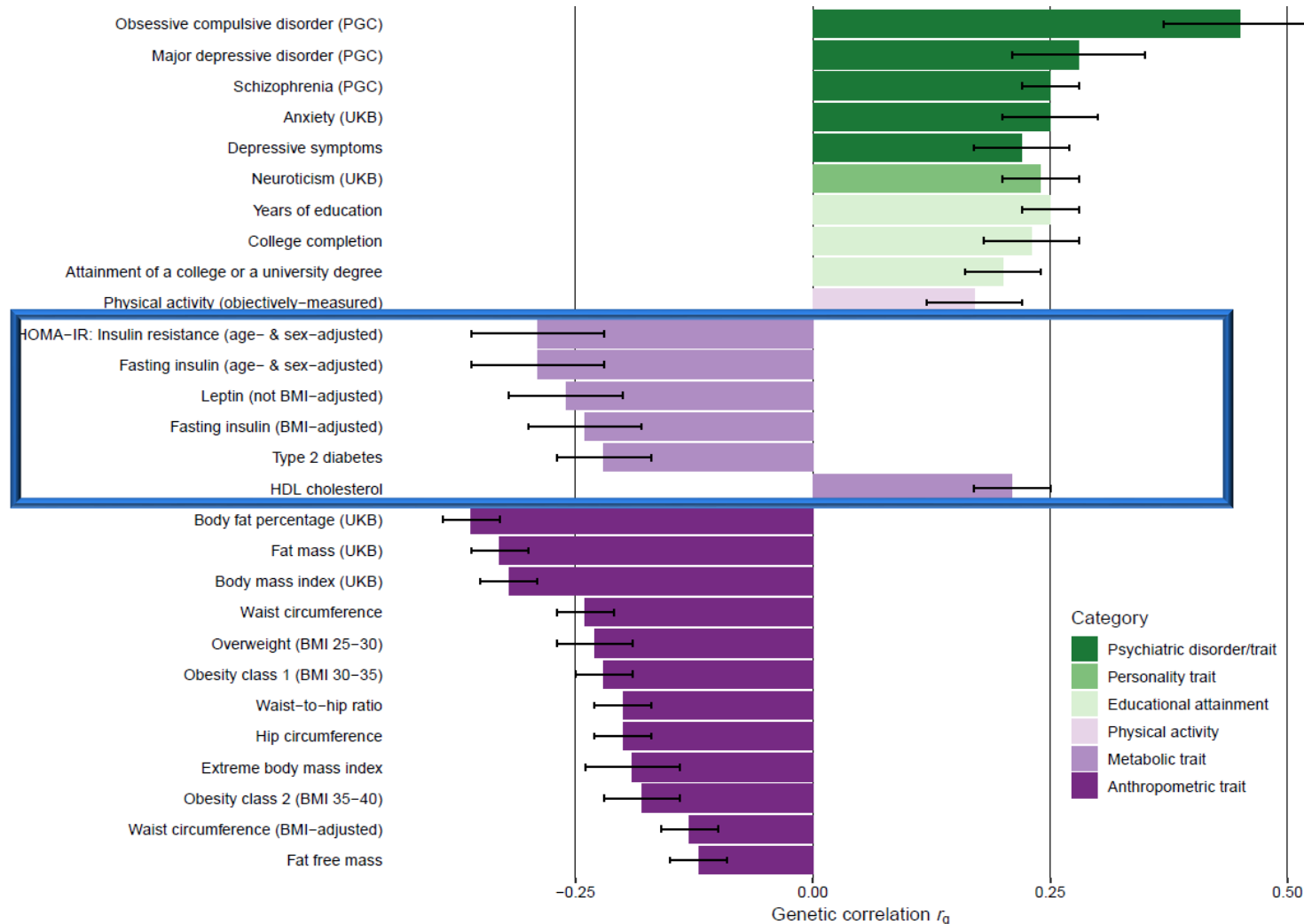
P 3

**ICD-11 and
DSM-5
recommend
5th centile
as cutoff**

Anorexia nervosa: BMI \leq 10th centile

Age (years)

Anorexia Nervosa: Metabo-Psychiatric Disorder



Bonferroni-significant genetic correlations (SNP- r_g s) and standard errors (error bars) between anorexia nervosa and other phenotypes as estimated by LD score regression

Only traits with significant P values following Bonferroni correction are shown. Correlations with 447 phenotypes were tested (Bonferroni-corrected significance threshold $P > 1.11 \times 10^{-4}$). PGC = Psychiatric Genomics Consortium, UKB = UK Biobank, HOMA-IR = Homeostatic model assessment - insulin resistance.

Improvements Noticeable Within 1-5 Days



IMPROVED SLEEP
IMPROVED MOOD
REDUCED INNER TENSION
REDUCED URGE TO MOVE **REDUCED**
IMPROVED SOCIAL INTERACTION
REDUCED PREOCCUPATION WITH FOOD
REDUCED WEIGHT PHOBIA
IMPROVED CONCENTRATION AND MEMORY
INCREASED APPETITE UND HUNGER
CONSTIPATION RELIEF
IMPROVED SKIN TURGOR
IMPROVED WOUND HEALING
INCREASED LEUCOCYTE COUNT

Current Implications for Treatment

■ Psychoeducation:

- Psychological effects of starvation
- Little improvement during initial weight gain
- Provide feedback on improvements during weight gain
 - Formalized test battery to allow patient/caregivers to track changes over time
- Weight gain represents means for the purpose
 - Adipokines, leptin
 - Slow initial increase in serum leptin

■ Relapse prevention

- Maintenance of a sufficiently high leptin level
- Avoid leptin dips
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Approved Medications for Feeding and Eating Disorders

Pica

-

Rumination Disorder

-

Avoidant Restrictive Food

Intake Disorder

-

Anorexia nervosa

-

Bulimia nervosa

Fluoxetine (EMA, FDA)

Binge-Eating-Störung

Lisdexamfetamine (FDA)



Primary Cognitions and Behavior

- Premorbid personality traits: e.g. ambitious, perfectionistic, shy/timid, conformist
- Premorbid mental disorders: e.g. feeding/eating disorders, major depression, anxiety disorders, OCD
- Covid-19 and triggers: e.g. social isolation, stress, anxiety, fewer rewards, boredom
- Conclusions:
 - Unremarkable premorbid mental health in many patients
 - Weight loss represents initial step
 - Different motivations trigger weight loss
 - e.g. to lose weight, excel, optimize health, improve environment
 - premorbid personality features entails higher commitment to pursuit



[https://chasingvibrance.com/7-ways-stay-motivated/;](https://chasingvibrance.com/7-ways-stay-motivated/)

<https://www.conserve-energy-future.com/practical-improvements-to-reduce-your-company-carbon-footprint.php>

Psychiatric Symptomatology in Different Hormone Deficiencies

Hormone	Psychiatric symptoms upon deficiency
Thyroid hormones	Fatigue, depression, hypersomnia, forgetfulness, inattention, mental slowness, emotional lability, reduced libido
Growth hormone	Fatigue, depression, anxiety, insomnia, reduced libido
Testosterone	Males: fatigue, depression, anxiety, reduced libido, anhedonia
Estradiol	Females: fatigue, depression, anxiety, insomnia
Cortisol	Fatigue, burnout, depression, reduced concentration, anhedonia

Successful Treatment of Leptin Deficiency with Recombinant Leptin



Prior to treatment

42 kg at 3 y



After treatment

32 kg at 7 y

**BUT:
Minimal
Effect on
Body Weight
in Obesity
Trials**

**Farooqi et al.,
NEJM 1999**



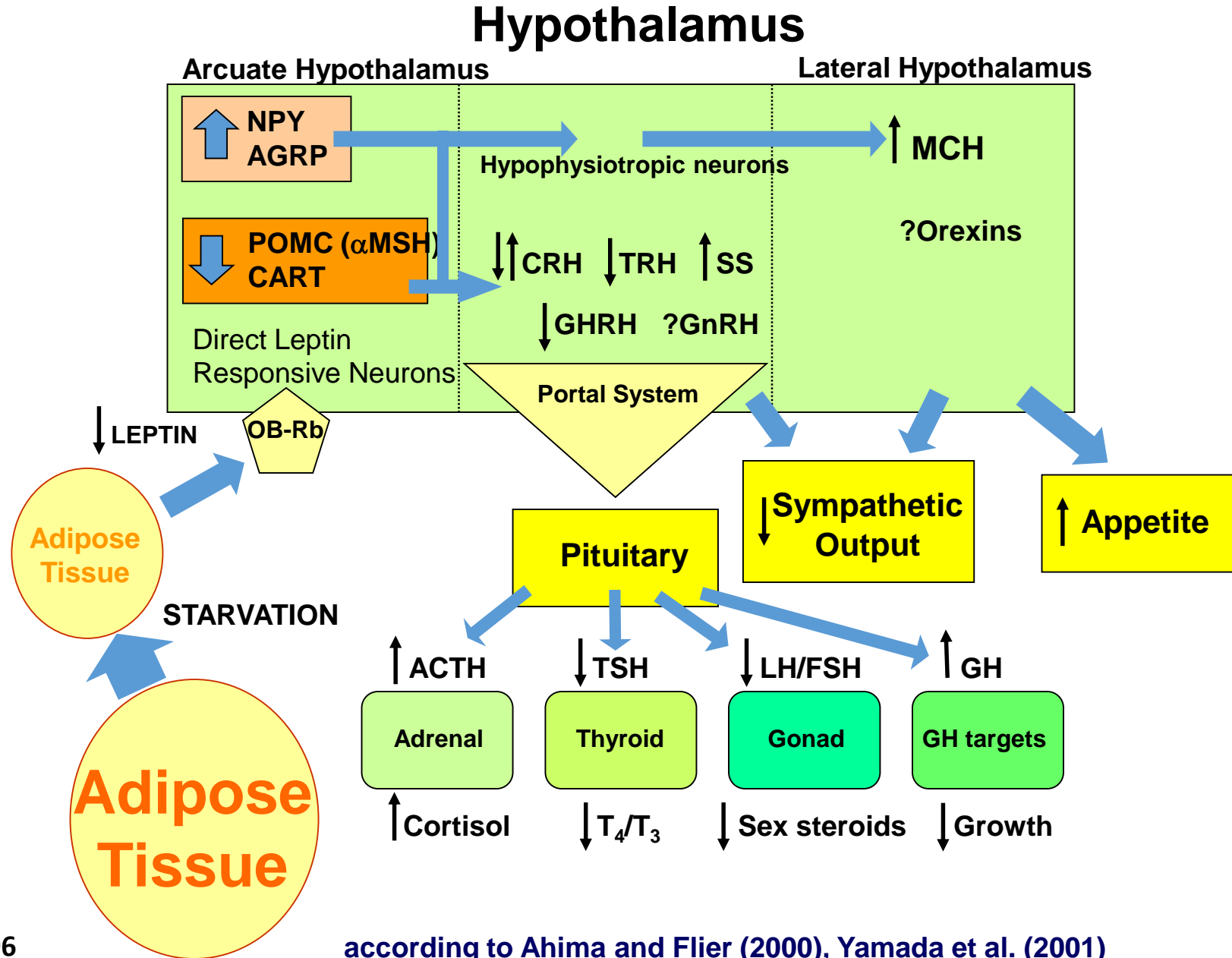
Zhang et al.,
Nature 1994

Leptin Signaling: Neuroendocrine Adaptation to Semi-Starvation

Prevention of starvation-induced drop in leptin substantially blunts changes in gonadal, adrenal and thyroid axes

In contrast, leptin repletion during starvation has little or no effect on body weight

*Regulation of neuroendocrine system during starvation:
Main physiological role of leptin?*



Leptin as the Major Signal for Adaptation to Starvation?

- **Extension of hypothesis of Ahima et al (neuroendocrine adaptation)**
- **Leptin receptors in most peripheral tissues and in many brain regions**
 - **Reproduction, liver and enteric metabolism, hematopoiesis, and immunity**
 - **Psychological/behavioral effects; reward system**
- **Starvation induces many somatic and mental changes**
 - **Leptin-mediated (indirect) effects via hypothalamus-pituitary-end organ-axes**
 - **Direct effects of leptin on peripheral and central tissues**
 - **Graded response to starvation via circulating leptin?**

Hypothalamic Amenorrhea: Treatment with Human Recombinant Leptin (Metreleptin)

- 8 females with hypothalamic amenorrhea of ≥ 6 months duration (mean: 5 years)
- 6 untreated controls
- Metreleptin (r-metHuLeptin) for three months
 - Increment of serum LH levels within 2 weeks
 - Increments of maximal follicle diameter, size of ovary and serum estrogen level within 3 months
 - 3 patients ovulated, 2 pre-ovulatory follicles
 - No significant weight loss; no side effects except reduction of appetite in third month of treatment

Leptin and Sweet Taste

Background

db/db mice: increased taste sensitivity; elevated preference for different sweet tastes as of day 7

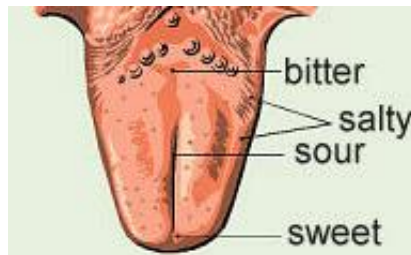
Methods

Reaction of receptor cells and peripheral nerves to different tastes prior to and after application of leptin

Results

Ob-Rb expressed in subpopulation of taste cells

Leptin inhibits selective reaction of taste cells to sweet substances (hyperpolarisation via potassium leakage)



Taste cells: peripheral target for leptin

Leptin suppresses perception of sweetening agents

Kawai et al. PNAS (2000) 97: 11044-49

The Barren Room (Patient T; AN, OCD, PTSD)

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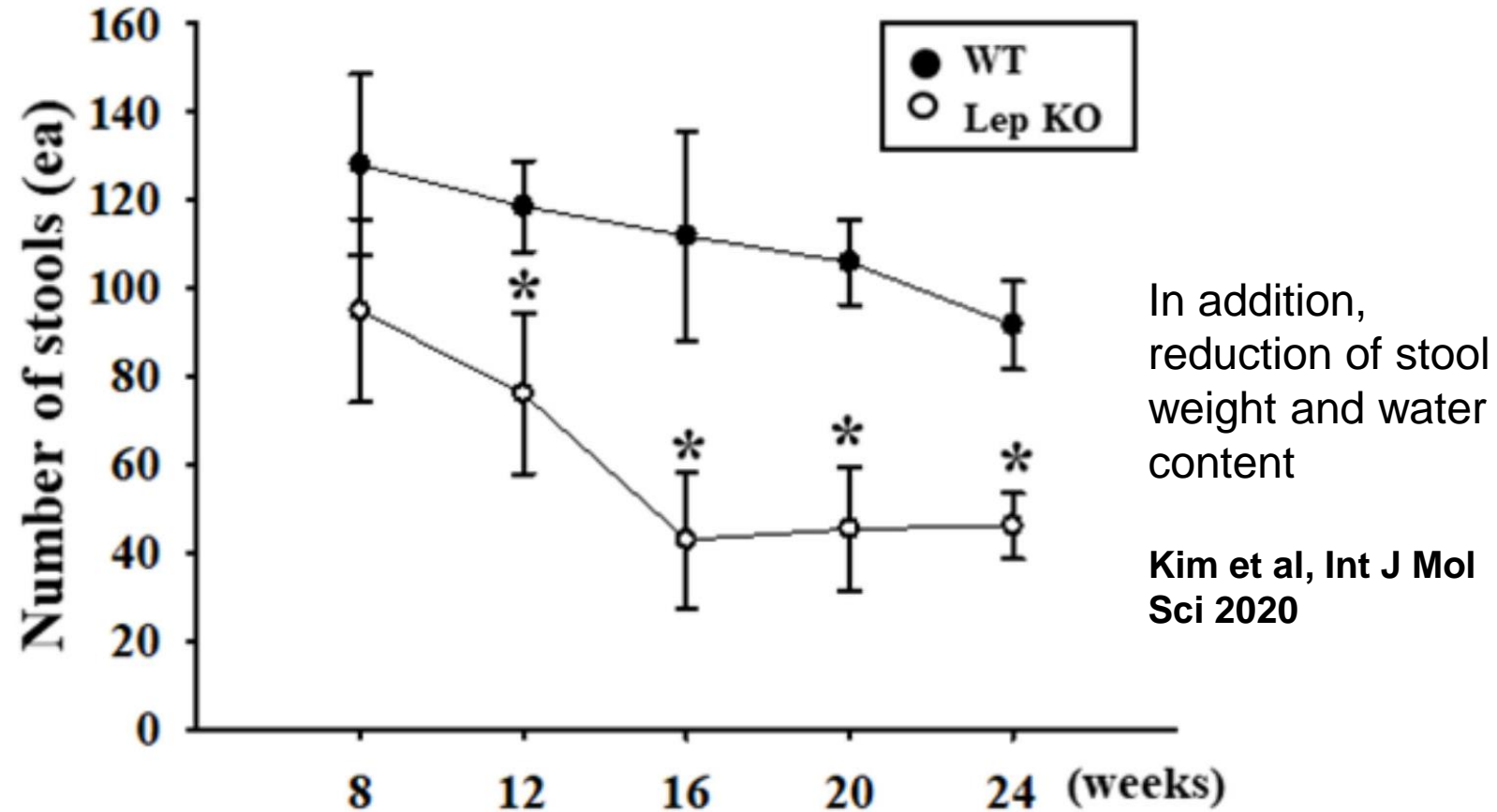
More and more I discovered and observed life outside, I began to like it, I wanted this life, too.

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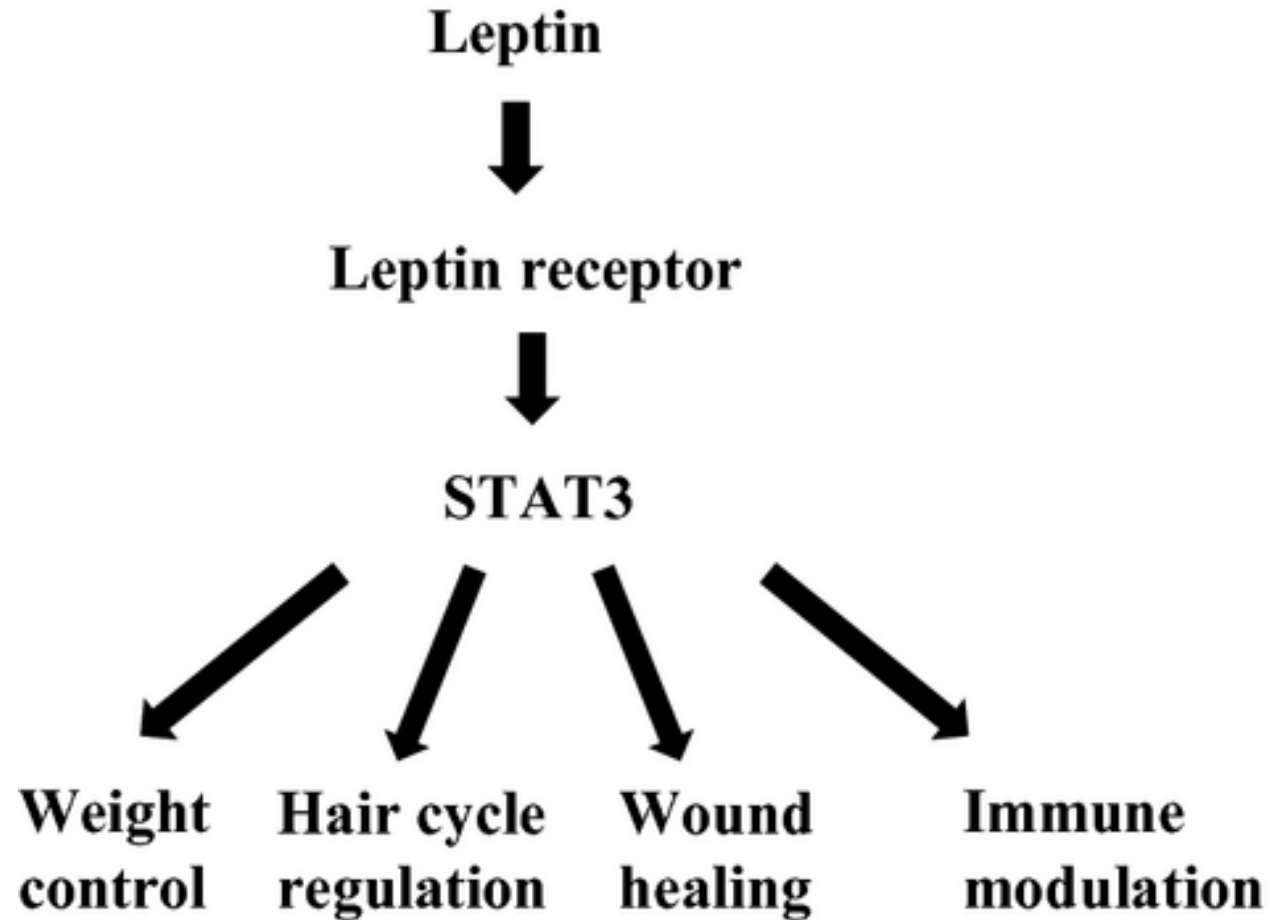
DeepL Translate

Peripheral Effect of Leptin: Constipation



Function and regulation of gastrointestinal motility via joint effects and communication of multiple cells (enteric neurons, smooth musculature, intestinal Cajal cells)

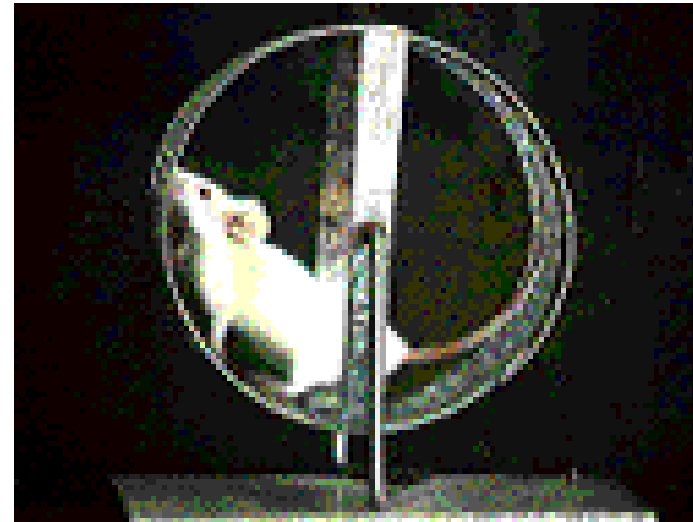
Other Peripheral Effects of Leptin



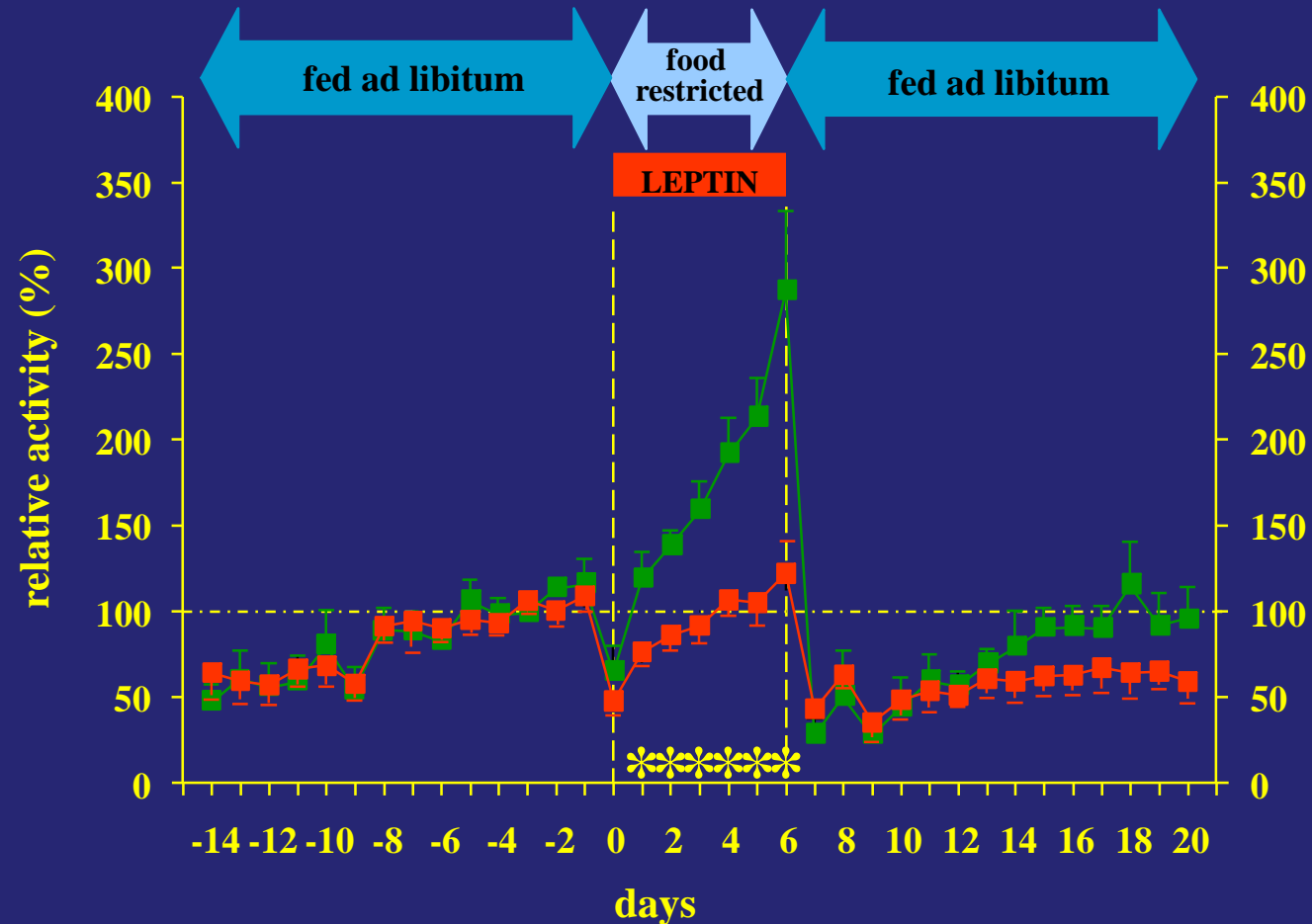
Semi-Starvation Induced Hyperactivity Anorexia Based Hyperactivity

**Caloric restriction entails
hyperactivity in rats**

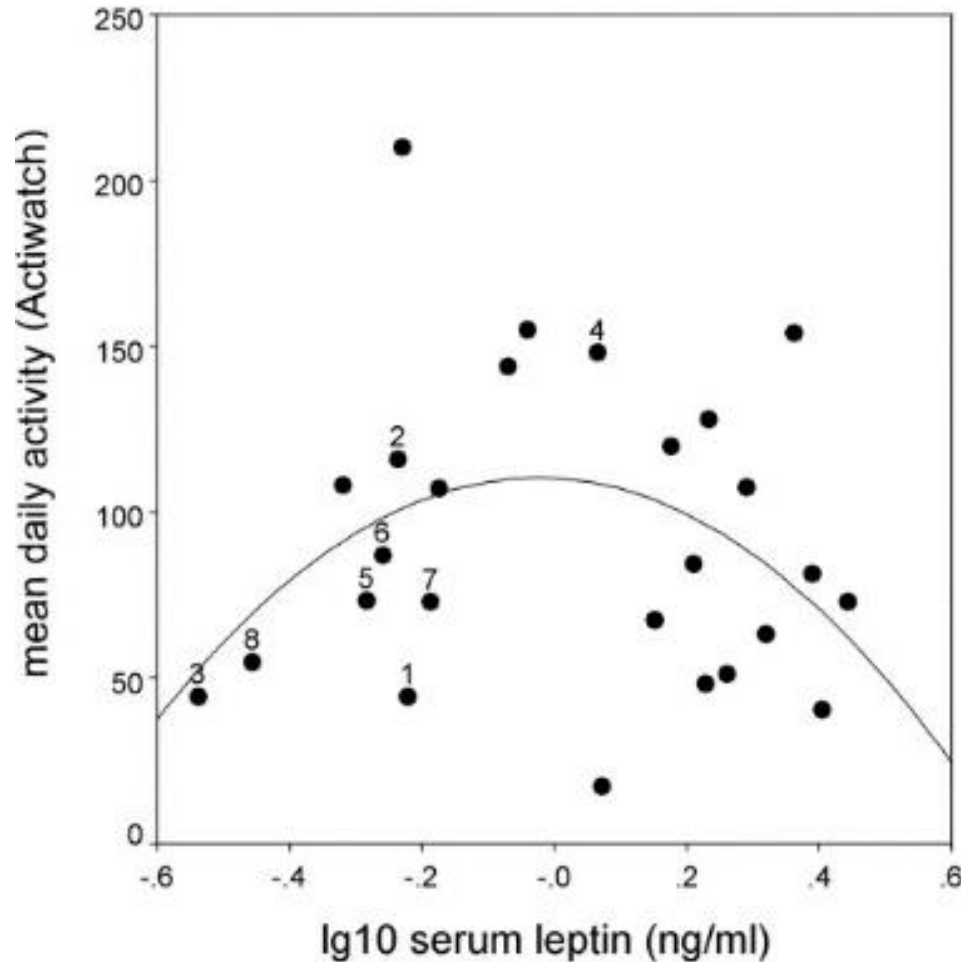
**Best known model for
anorexia nervosa**



Leptin Suppresses Semi-Starvation Induced Hyperactivity



Anorexia nervosa: Inverted U-Shaped Relationship between Physical Activity and lg10 Serum Leptin Levels



Clinical implications:

- 1) A leptin threshold must be surpassed for hyperactivity to decline
- 2) Some patients develop hyperactivity during weight gain
- 3) No hyperactivity in severe underweight

Relationship between Mood and Serum Leptin Level

Patient/proband groups

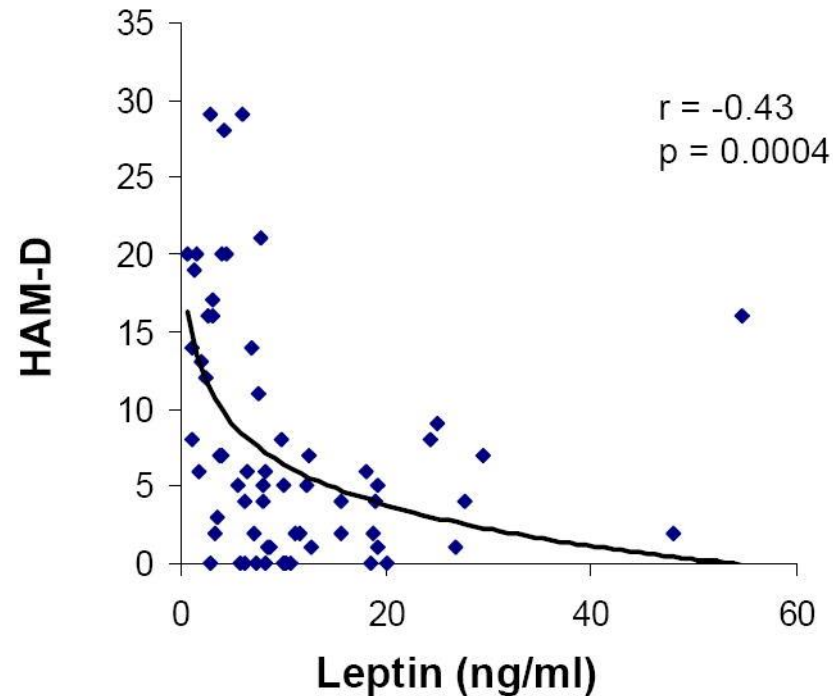
AN N=15

Hypothalamic Amenorrhea N=12

Obesity N=17

Healthy Controls N=20

A.



Hypothesis

Hypoleptinemia Responsible for Mental Symptoms of Starvation

- **Hormone deficiencies entail mental health impairments**
 - **Hypothyroidism: forgetfulness, fatigue, mental slowness, inattention, and emotional lability, depression**
 - **Hypocortisolism: fatigue, depression, reduced concentration**
 - **Growth hormone deficiency: emotional instability, reduced energy, insomnia, reduced libido**
 - **Hypoaldosteronism: fatigue, depression, altered state of mind**
 - **Hypoparathyroidism: anxiety, irritability, depression, psychosis**
- **Suppression of starvation induced hyperactivity in rats**
- **Behavioral findings in rodents: *ob/ob* mice, wildtype mice**

Treatment of Anorexia Nervosa with Leptin

■ Amryt Pharmaceuticals:

- Portfolio of drugs for patients with orphan diseases

- Metreleptin approvals

- FDA (2014; Myalept®): generalized lipodystrophy (GL) and congenital leptin deficiency

- EMA (2018; Myalepta®): GL and treatment resistant partial lipodystrophy

■ Hypothesized effects in AN

- Hyperactivity

- Additional beneficial effects on mood, eating disorder specific cognitions?

- Addiction hypothesis: Starvation no longer perceived as beneficial?



Case studies

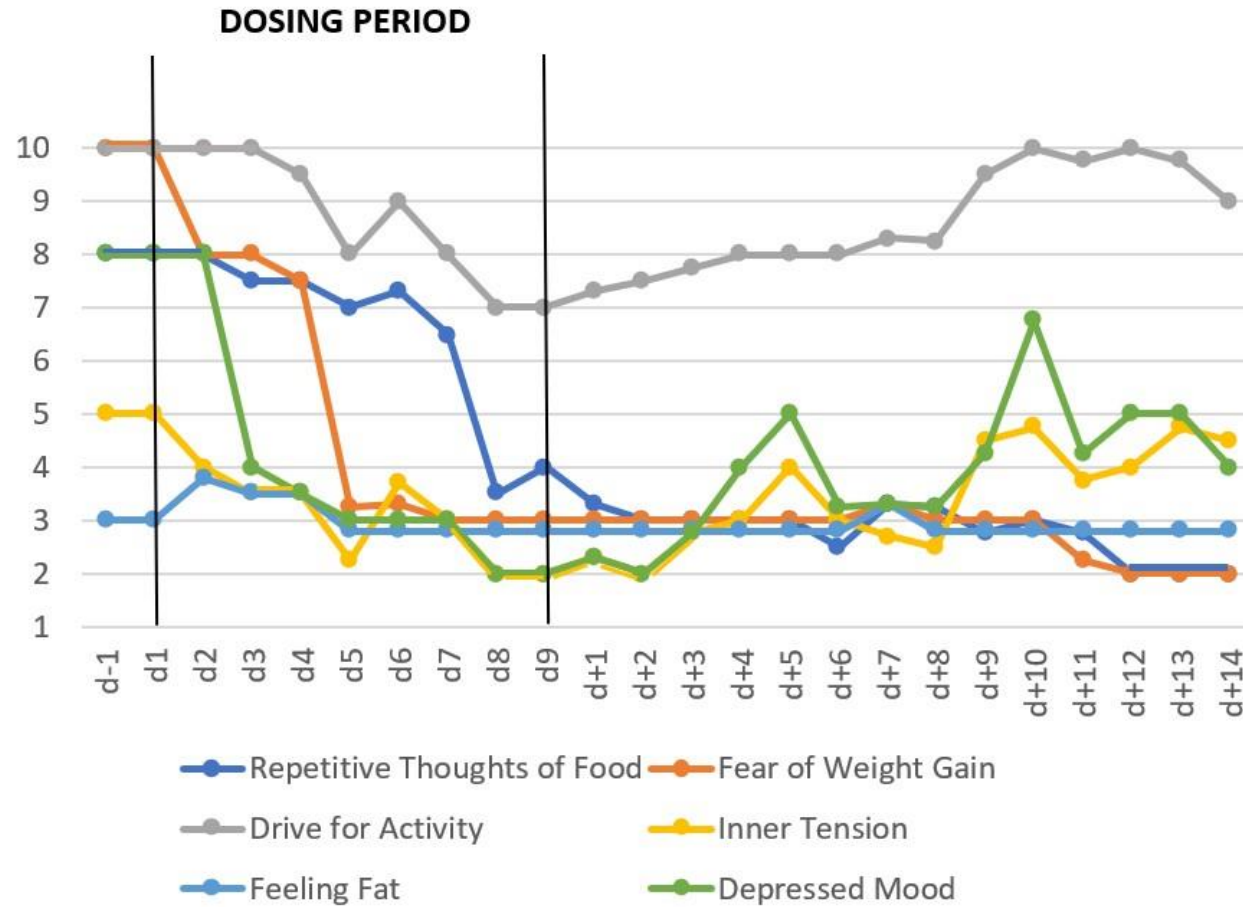
- **14 patients (2 males; 5 published cases) treated in 5 hospitals**
- **Standard treatment: eating plan; psychotherapy, co-medication on individual basis**
- **Inclusion criteria for off-label metreleptin**
 - **Severe AN**
 - **Written informed consent (patients/parents)**
- **Individual dosing during clinical observation**
 - **Dosing periods mostly between 6 and 24 d**
 - **1 patient 80 d, 1 patient with comorbid partial lipodystrophy 5 months**
 - **Dosages between 3 and 10 mg/d**

Single Case Observations: Metreleptin in Anorexia Nervosa

- **No SAE**
- **Rapid onset of pronounced improvements:**
 - **Improvement of sleep**
 - **Less preoccupation with food**
 - **Antidepressant effect**
 - **Reduction of inner tension, reduced urge to move**
 - **Improved social interaction**
 - **Less fear of weight gain**
 - **Increased (!) hunger, less fullness**
 - **Less constipation**

VAS Self-Rated Key Cognitions and Emotions

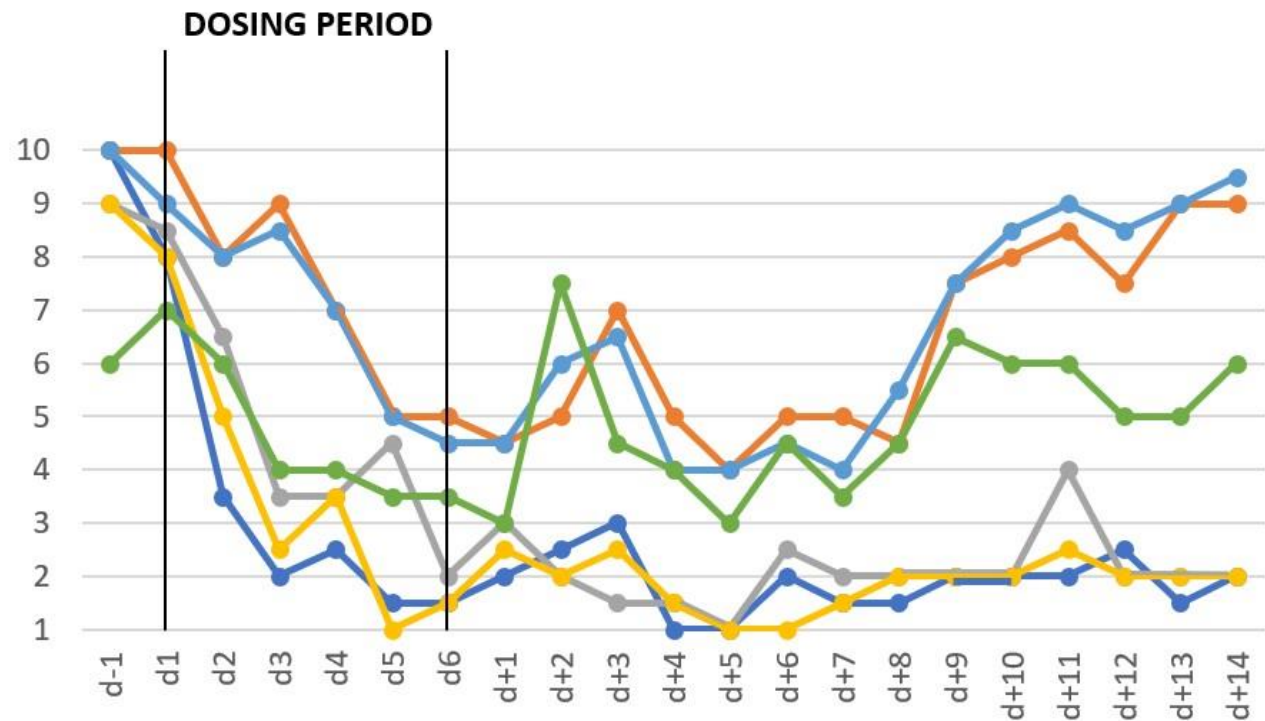
Patient A



Visual analogue scales (1-10) filled in twice or thrice daily
Means for items

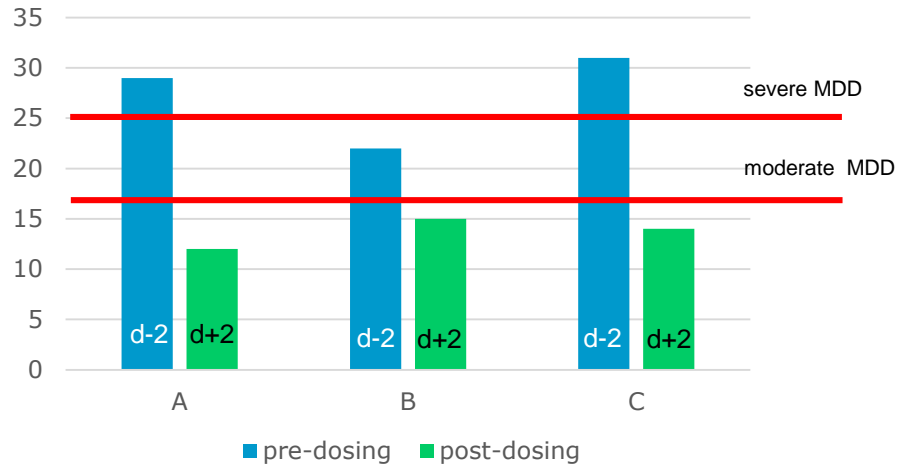
VAS Self-Rated Key Cognitions and Emotions

Patient C

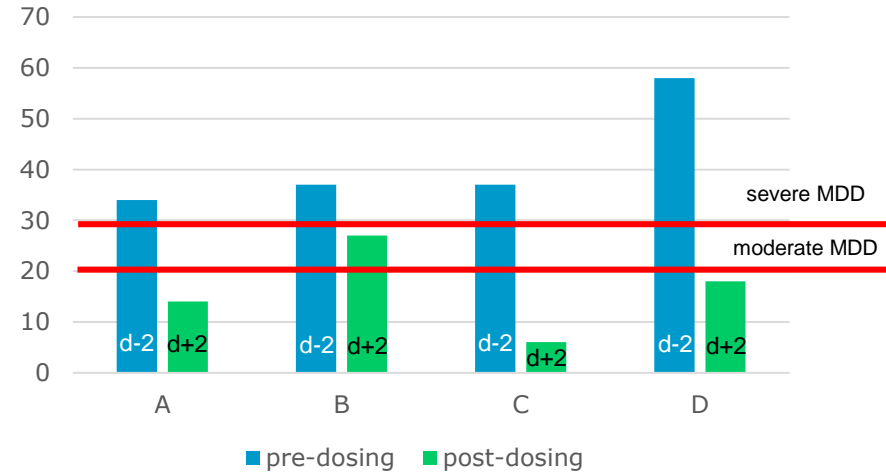


Expert and Self-Rated Depressive Symptoms

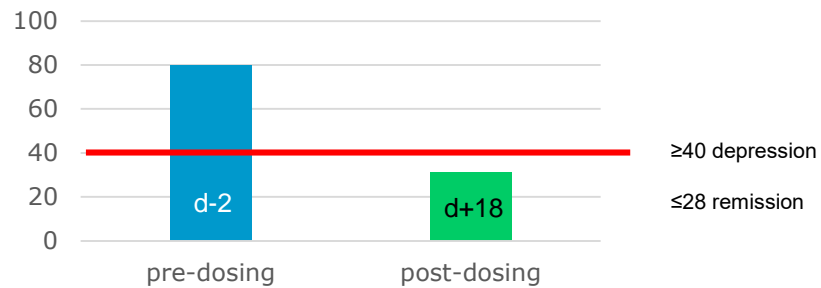
HAMD-17 Score; Patients A - C



BDI-II Score; Patients A - D



CDRS-R score; Patient D



Dosing period (days):

A=9

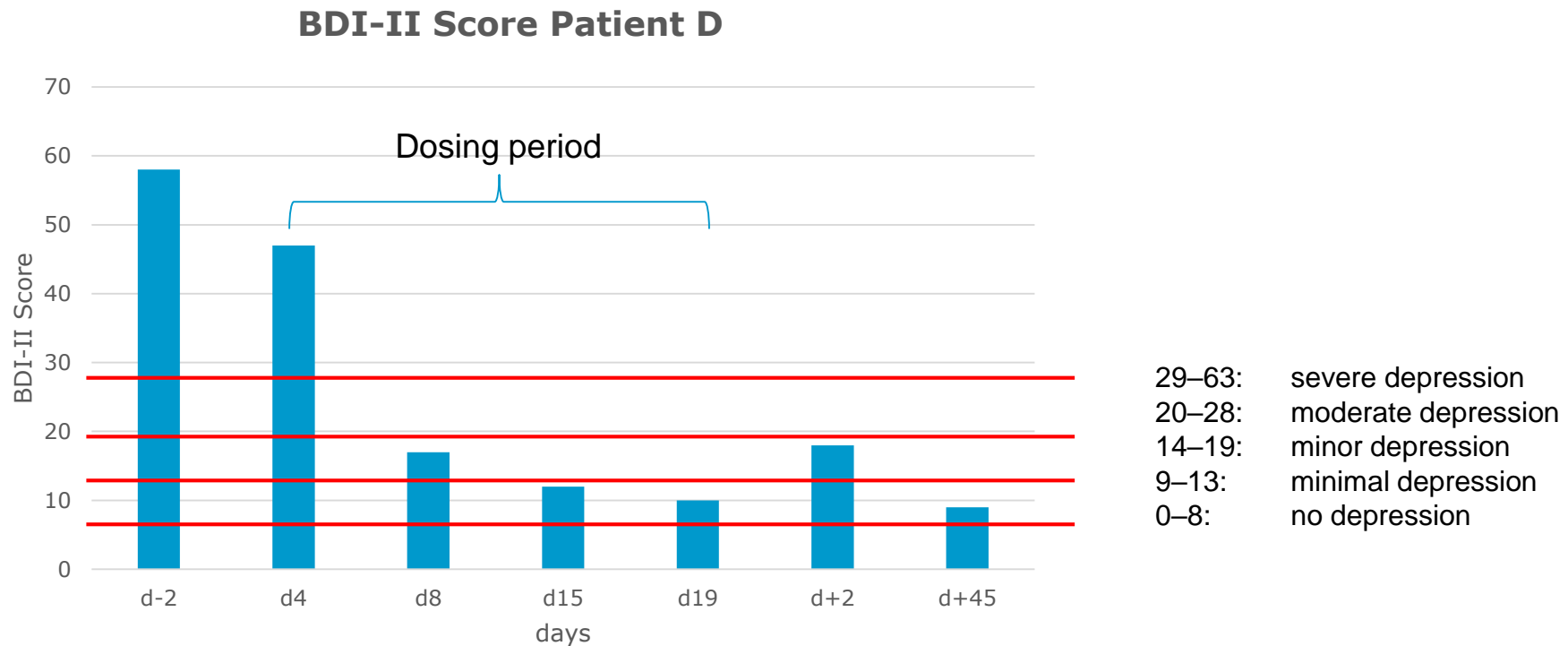
B=14

C=6

D=24

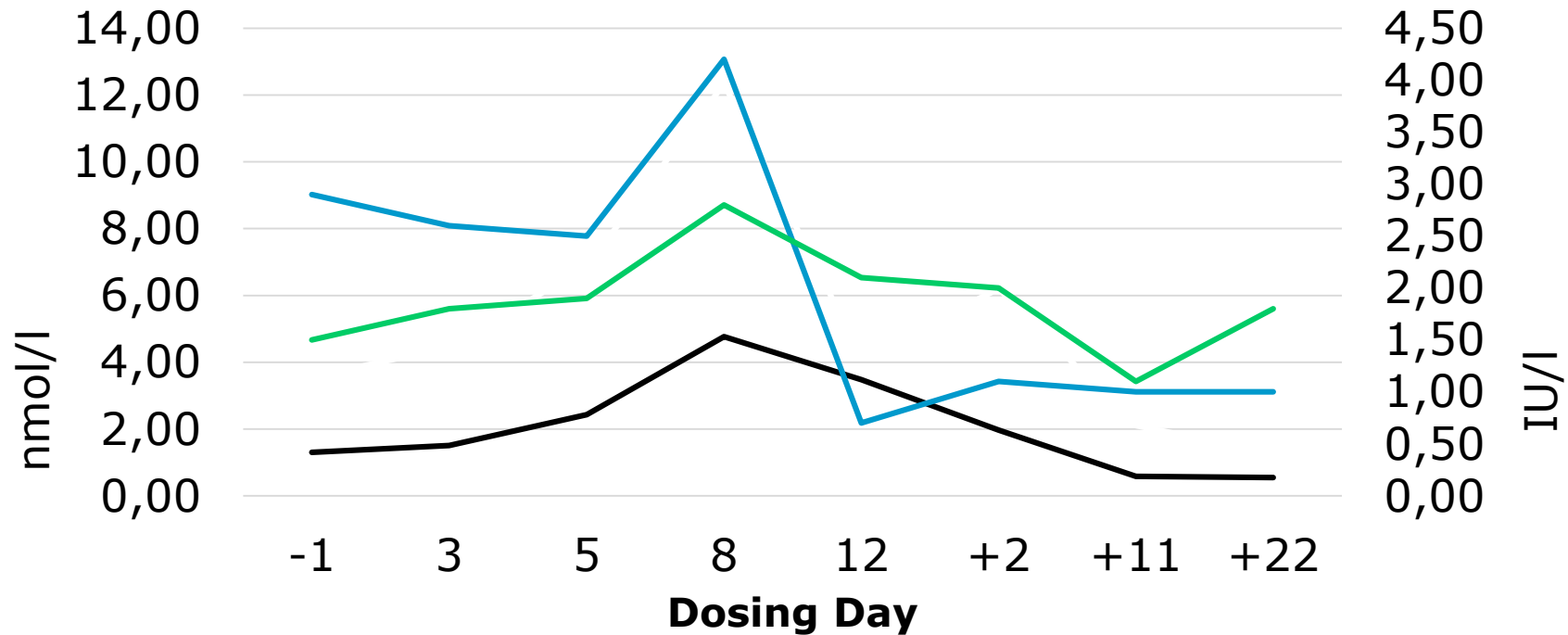
BDI-II: Beck & Steer 1987; HAMD-17: Hamilton 1960; CDRS-R: Keller et al. 2001

Self-Ranked Depressive Symptoms in Patient F up to 45 days after End of Dosing Period



BDI-II: Beck & Steer 1987

Increased Serum Levels of FSH, LH and Testosterone During Metreleptin Dosing in Male Patient F



—bioavailable Testosterone (nmol/l) —LH (IU/l) —FSH (IU/l)

Patient F: Parental Observations/Comments - Dosing Days 1 to 17

... stopped permanent crying, laughed for the first time for more than six weeks ...

... became clear in his thoughts and expressions, smiled a lot ...

... showed very good mood and made jokes ...

... allowed huggings and kept smiling ...

... reduced compulsivity (time spent running, showering) ...

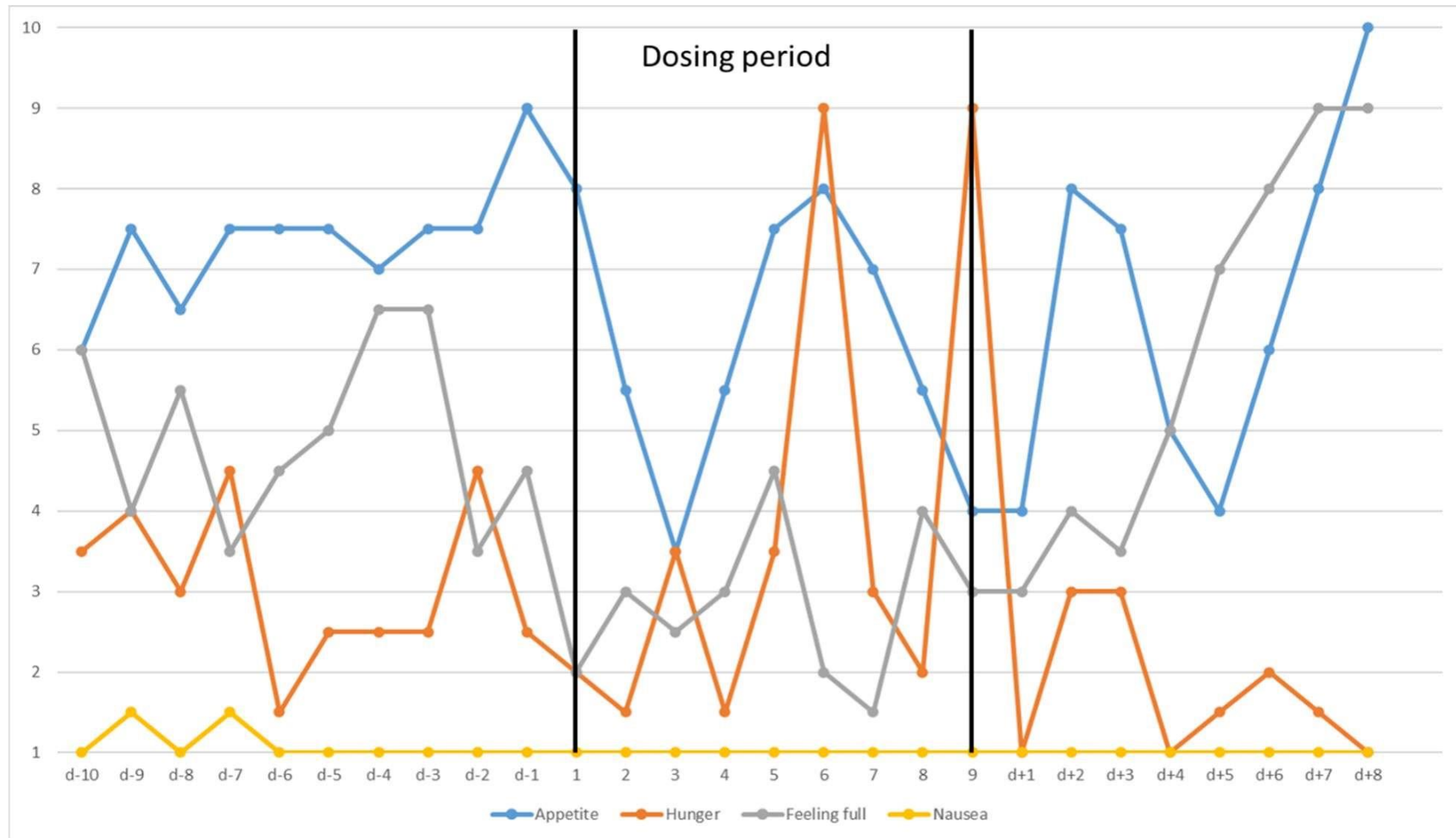
... mentioned that his drive for activity was reduced ...

... open for topics other than ED related for the first time in a long time ...

... his former personality is re-appearing ...

... thanks for bringing our son back to us ...

Patient R: VAS Ratings of Appetite and Hunger



Maternal account: Patient R

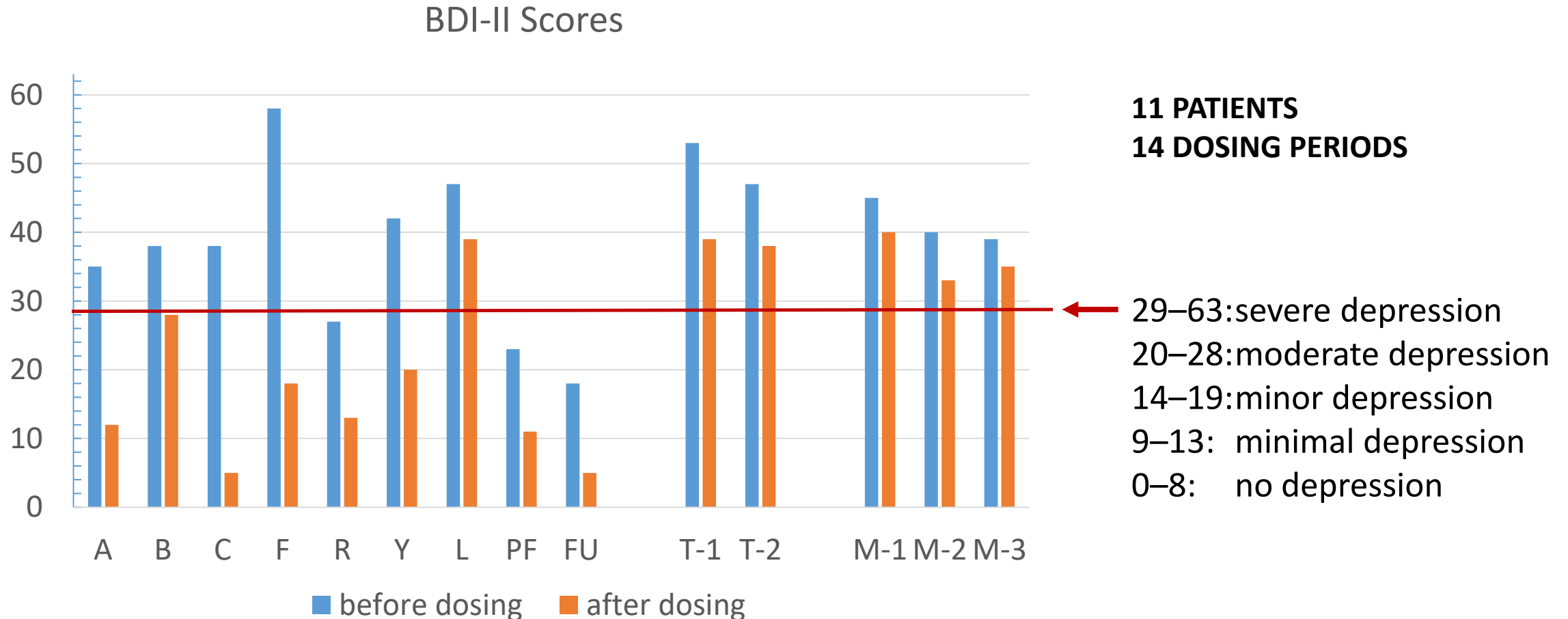
- **Severe AN with fixations during prior inpatient treatment for feeding**
- **Metreleptin for 8 days, 7 X 6mg, 1 X 3mg**
- **Antidepressant effect noticeable to the patient as of dosing day 3**
- **Hunger increased during treatment, fullness decreased**
- **Subsequent daily phone contacts for 3-5 minutes for 3 weeks to reintroduce foods**
- **Weight gain of 20 kg (to 60 kg; 87th BMI centile)**
 - **premorbid overweight (\approx 85th BMI centile) and maternal obesity**

R has made tremendous progress! 😊 Her **mood is usually positive** and she has lots of energy. She can attend school without any problems, because she eats an extended breakfast at seven. For long school days she takes care to bring ample food supplies to school, which she can eat in the presence of her peers. When she comes home, she is **HUNGRY !** Even when I cannot accompany her at meals, she manages to prepare and eat her food herself. She really does an excellent job! I have now allowed her to participate in gymnastics and judo lessons, because she has intermittently reached her premorbid body weight.

I am so happy that you enabled her to open up this damned cage door. I just cannot sufficiently express my gratitude.

Several people have noticed that R is **much more content and open for contacts**.

PATIENT SELF-RATINGS FOR DEPRESSION



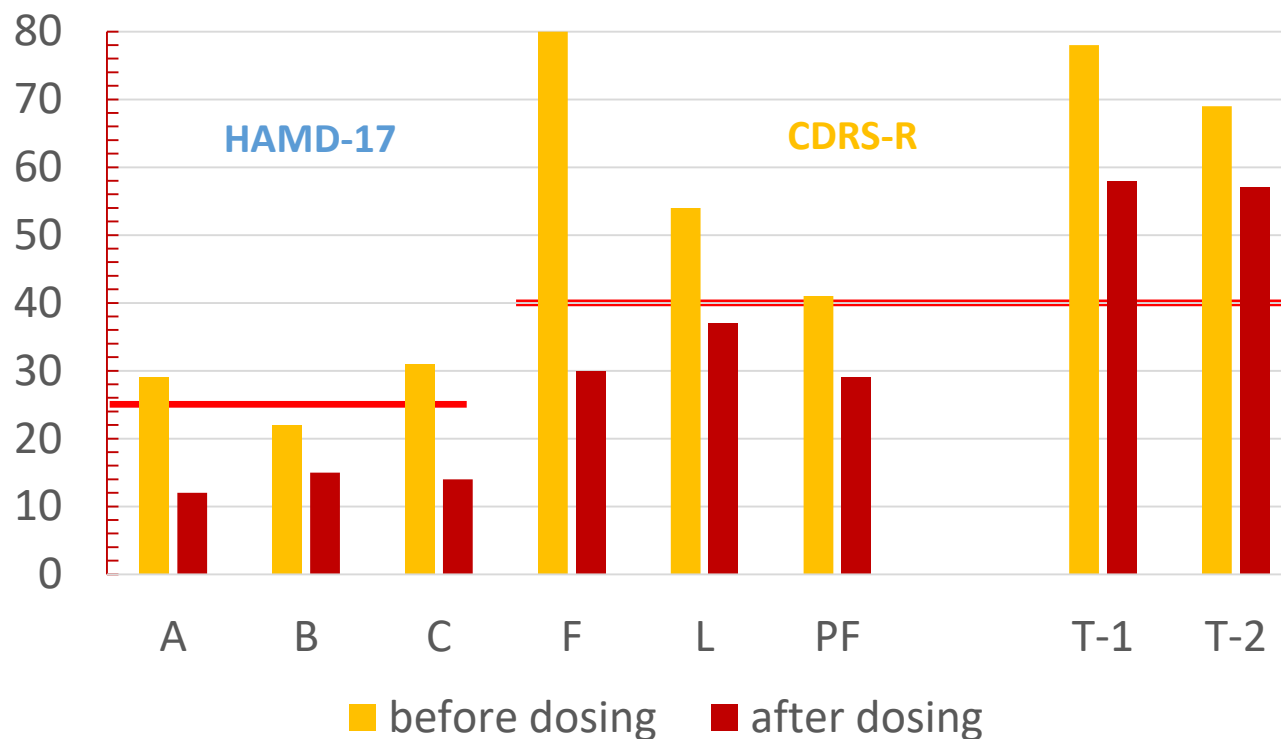
National Institute for Health and Care Excellence (NICE) suggest difference of ≥ 3 BDI-II points is a clinically significant treatment effect for normal depression (mental health guidelines developed by the National Collaborating Centre for Mental Health, 2004)

EXPERT (CLINICIAN) RATINGS

HAMD-17 scores

- ≥ 25: severe depression
- 17–24: moderate depression
- 9–16: minor depression
- 9–13: minimal depression
- 0–8: no depression

Clinician rated HAMD-17 (adults) or
CDRS-R raw score (adolescents)



**11 PATIENTS
7 TIMES RATED
BY HAMD OR CDRS-R**

CDRS-R scores

- ≥40 depression
- ≤28 remission

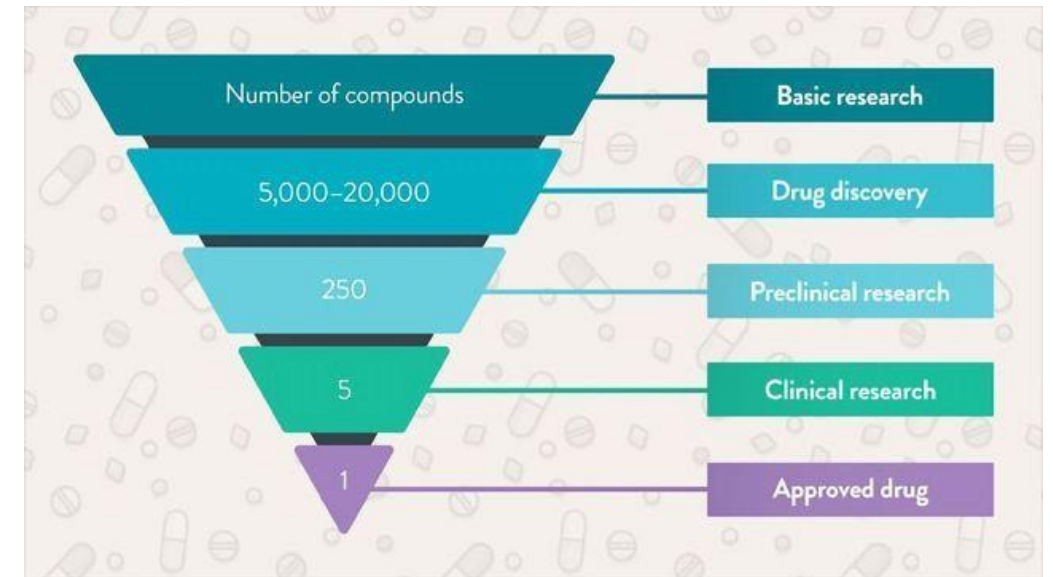
Placebo Effects?



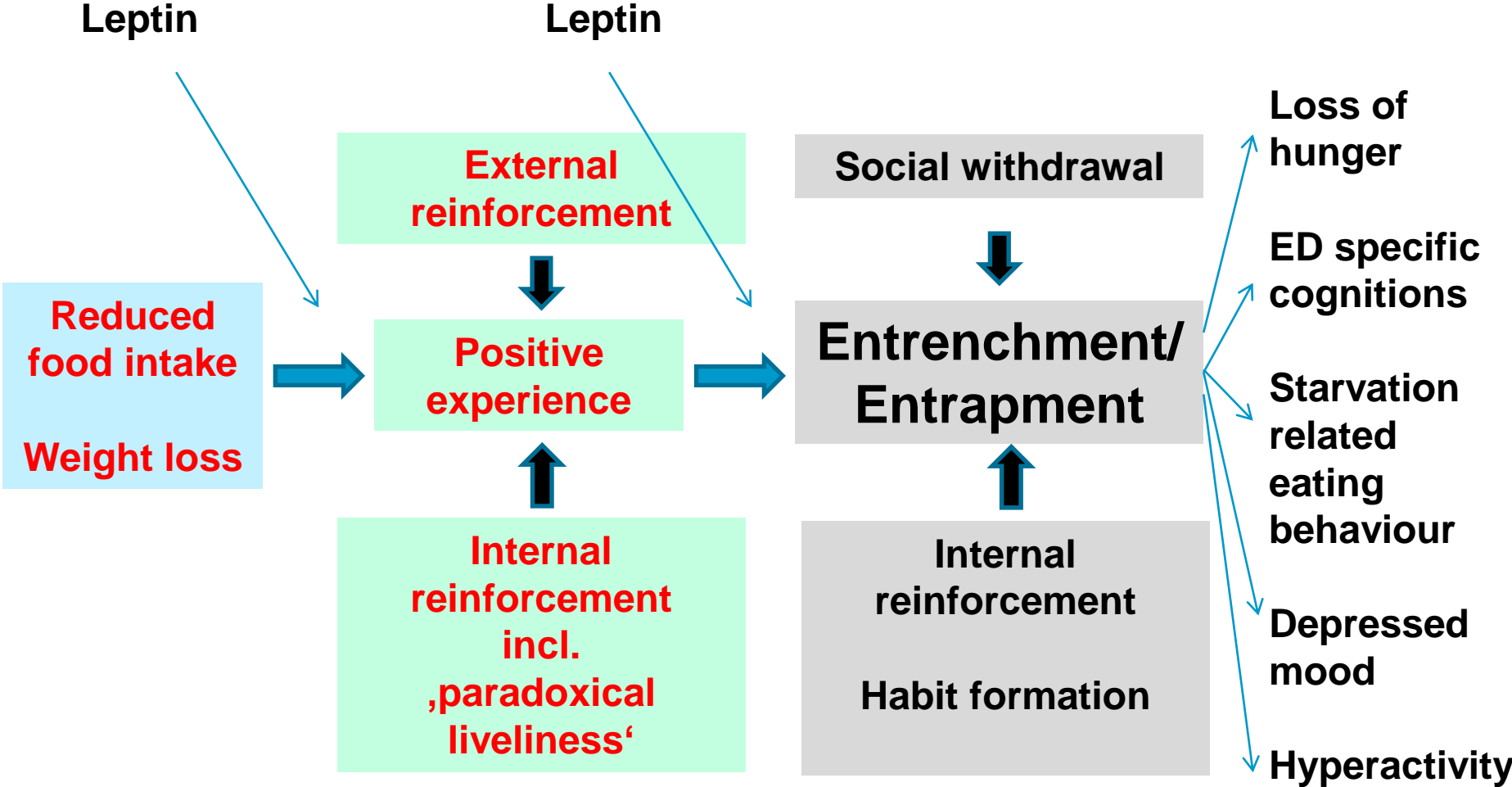
- **No medication licensed for AN; no evidence for strong placebo effects in RCTs**
- **Observed improvements partially not covered in informed consent**
 - E.g. constipation, increased hematopoiesis, reduction of inner tension, improved sleep
- **Homogeneous improvements: reduced preoccupation with food, improved mood, increased concentration and social contacts**
 - More subtle effects on concentration and social interaction
 - Inter-individual temporal patterns very similar
- **Age independency**
- **Independent of premorbid weight**
 - Hypothesis: effects on appetite and hunger in patients with high premorbid BMI
- **Somatic and mental improvements consistent with current knowledge of the effects of leptin**
- **Hypothesis driven approach**
- **Mood improvement in patients with lipodystrophy treated with metreleptin (Vieira et al. Obes Facts 2022)**
- **Evidence for mood improvement in patients with congenital leptin deficiency (Hebebrand et al. Obes Facts 2022)**

Problems Inherent to Development of Novel Drugs

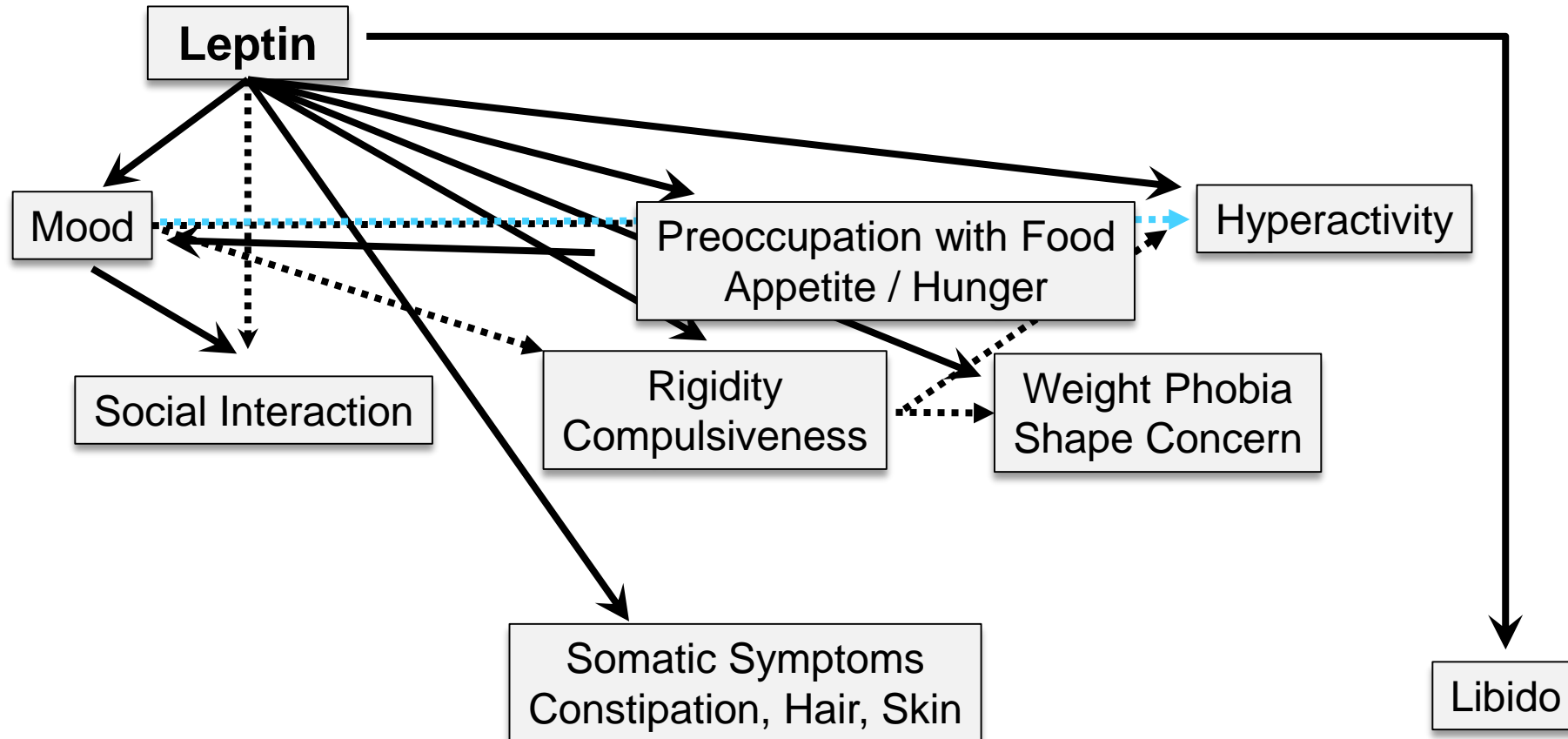
- **Belief in psychogenic / psychodynamic etiology**
- **Limited neurobiological research**
- **Limited pipeline/portfolio of drugs**
- **Few solid hypotheses**
- **Dependence on chance findings**
- **Pharmaceutical industry: eating disorders are not a focus**
- **High costs for drug development up to approval**
 - **Current estimate: 1.1 – 1.6 billion \$**
 - **80-120 million \$ for repurposing**



Lost in Anorexia Nervosa Hormone Deficiency Disorder?



Metreleptin Reverses Starvation-Induced Adaptations: Central and Peripheral Effects and Potential Relationships



DSM-5 Criteria

B) Intense fear of gaining weight or becoming fat, or *persistent behavior that interferes with weight gain*, even though at a significantly low weight

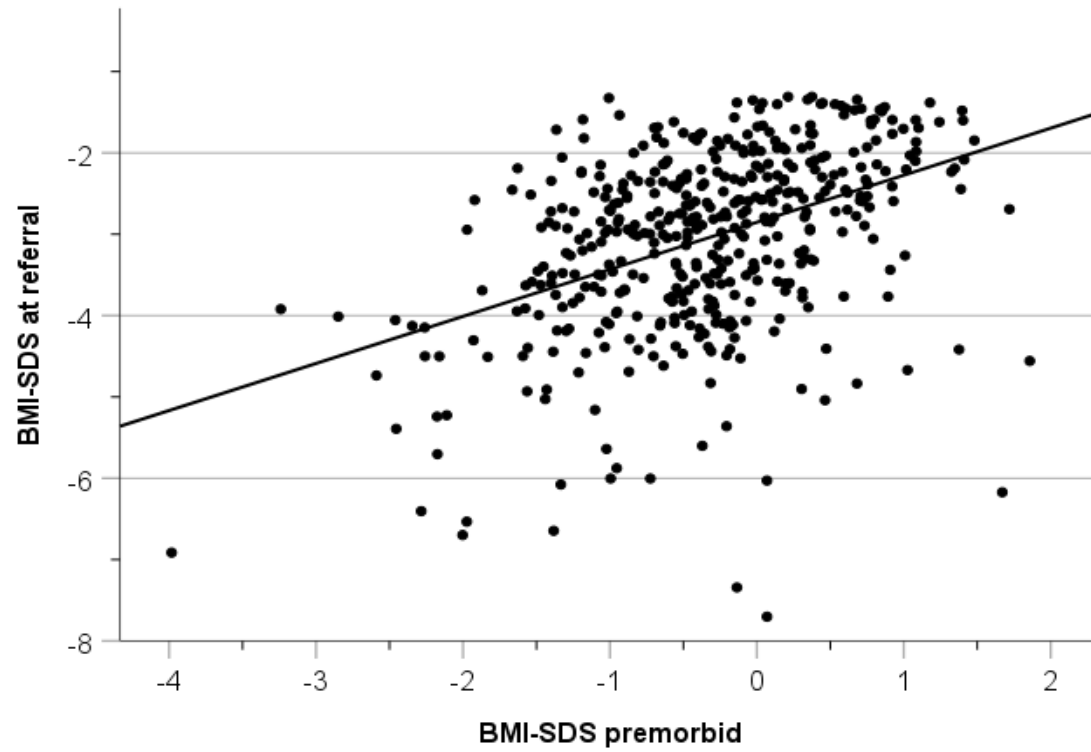
C) Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or *persistent lack of recognition of the seriousness of the current low body weight*

DSM-5 Criteria for Atypical Anorexia Nervosa

Other Specified Feeding and Eating Disorder

All of the criteria for AN are met, except that despite significant weight-loss, the individual's weight is within or above the normal range

associated with characteristic psychological symptoms of AN including overconcern with shape and weight, frequent comorbid depression, somatic complications such as hypotension and bradycardia and menstrual disturbances



Loose Strings

- **Leptin - hormone with profound effects on psychological well-being?**
- **Psychopharmacological effects of leptin only in starved humans?**
- **Duration of treatment, dosage?**
 - **Single patients with ≥ 2 dosing episodes**
- **Low versus high response rate**
 - **Suggestive evidence for lower effects in severely underweight patients (BMI < 13 kg/m²)**
- **Sex dependent regulation of leptin with pronounced differences during puberty**
 - **Explanation for female predominance and manifestation age for eating (and affective) disorders?**
- **Why are some patients more resistant than others?**
 - **Comorbidity, duration of the disorder, motivation, psychological and metabolic mechanisms**
- **High price of metreleptin: treatment costs ≈ 1300 Euros/d**
- **Can „starvation neurosis“ be treated with leptin analogs?**
- **Urgent need for RCTs and involvement of pharmaceutical industry**
- **Support from patient and parent groups**

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- **Patients**
- **Parents**

