Anorexia Nervosa: What’s New about an Old Illness?

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Conflict of Interest Disclosure

In the last 12 months, Dr. Walsh has received research support from:

AstraZeneca
The plan...

• Review the basics, including DSM-5
• Very brief update on epidemiology and treatment
• The enigma of persistence:
  – A new model
Acknowledgements

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• experimental subjects
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• input from many colleagues  
  (esp. Daphna Shohamy & Karin Foerde)
• Eating Disorders Research Unit at Columbia/NYS Psychiatric Institute  
  (esp. Joanna Steinglass)
Anorexia Nervosa: An Old Illness

1350  St. Catherine of Siena
1689  Richard Morton
1874  William Gull
1873  Charles Leseque

Holy Anorexia?
“Nervous Consumption”
“Anorexia Nervosa”
“Hysterical Anorexia”
Anorexia Nervosa
Key Diagnostic Features

• Relentless pursuit of thinness
• Fear of becoming fat
• Significantly underweight
DSM-5: ANOREXIA NERVOSA

A. Restriction of energy intake relative to requirements leading to a significantly low body weight in the context of age, sex developmental trajectory, and physical health. *Significantly low weight* is defined as a weight that is less than minimally normal, or, for children and adolescents, less than that minimally expected.

B. Intense fear of gaining weight or becoming fat, or persistent behavior to avoid 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 shape or weight on self-evaluation, or *persistent lack of recognition* of the seriousness of current low body weight.

Current subtype: Restricting vs. Binge/Purge

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# Anorexia Nervosa

## Associated Features

<table>
<thead>
<tr>
<th>Behavioral</th>
<th>Physiological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsession with food</td>
<td>Hypothermia, bradycardia, hypotension</td>
</tr>
<tr>
<td>Peculiar eating</td>
<td>Lanugo</td>
</tr>
<tr>
<td>Binge eating</td>
<td>Edema</td>
</tr>
<tr>
<td>Laxative/diuretic abuse</td>
<td>Anemia, leukopenia</td>
</tr>
<tr>
<td>Compulsive behavior</td>
<td>Increased LFT’s</td>
</tr>
<tr>
<td>Depression</td>
<td>Low estrogen, LH, FSH</td>
</tr>
<tr>
<td>Social isolation</td>
<td>Low-normal T4</td>
</tr>
<tr>
<td>Increased physical activity</td>
<td>High cholesterol</td>
</tr>
<tr>
<td></td>
<td>Decreased brain mass</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>
Minnesota “Starvation” Experiment 1944
Anorexia Nervosa: Long-Term Outcome

- Full Recovery: 1/3 to 1/2
- Death: 5% per decade of follow-up
- Alive but not well: the rest
- Obesity?: rare
Epidemiology of Anorexia Nervosa

• Lifetime prevalence among females 1-2%.
• 12 month prevalence ~0.5%.
  ~1/10th as frequent among males.
• Incidence (# new cases/year) has probably not changed dramatically in the last 40 years.
Treatment Update
Treatment of Anorexia Nervosa

• **Weight Gain is Essential**
  ~4000 kcals above maintenance per pound gained
  Intensive & structured care usually successful
  Parenteral methods rarely needed

• **Psychotherapy?**

• **Medication?**
Anorexia Nervosa
Proposed Treatments

- Thyroid Hormone
- ACTH
- Lobotomy
- ECT
- Chlorpromazine
- + Insulin
- Amitriptyline
- Lithium
- Phenoxybenzamine
- Domperidone
- THC
- Cyproheptadine
- Fluoxetine
- Olanzapine

- Psychoanalysis
- Individual therapy
- Family therapy
- Behavior therapy

Therefore, controlled studies are essential!
Anorexia Nervosa: Psychological Treatment

- **For younger patients:**
  the ‘Maudsley’ method

- **For older patients:**
  CBT?
  Non-specific clinical management?
The ‘Maudsley’ Intervention
Russell et al, 1987; Lock et al, 2001; Lock & leGrange, 2005

• Outpatient weight-gain treatment

• Twenty sessions over 6-12 months

• Puts the PARENTS in charge of the refeeding process (appropriate control, ultimately relinquished), contrary to traditional clinical recommendation of “parentectomy”

• Makes no assumption about etiology of AN
Treatment of Adolescents: “Maudsley” vs Individual Therapy

Figure 2. Observed partial and full remission rates by treatment assignment (end of treatment [EOT]; adolescent-focused individual therapy [AFT], n=49; family-based treatment [FBT], n=50; 6-month follow-up: AFT, n=47; FBT, n=44; and 12-month follow-up: AFT, n=49; FBT, n=45).

Lock et al., 2010
Psychotherapy for Adult Outpatients with AN

McIntosh (2005)

Touyz (2013)

Zipfel (2013)

BMI (kg/m²)

Baseline End of Treatment

CBT IPT NSCM

Baseline End of Treatment

CBT SSCM

Baseline End of Treatment

CBT Dyn TAU

Baseline End of Treatment
Anorexia Nervosa: Controlled Trials of Medication

- Antidepressants
- Antipsychotics
- Serotonin Antagonists
- Lithium
- THC
- Cisapride
- Zinc
# Anorexia Nervosa: Controlled Trials

<table>
<thead>
<tr>
<th>Class</th>
<th># Trials</th>
<th>Medication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>4</td>
<td>CMI, AMI (2), FLX</td>
<td>-</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>2</td>
<td>Sulpiride, Pimozide</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine</td>
<td>+</td>
</tr>
<tr>
<td>Serotonin Antagonist</td>
<td>3</td>
<td>Cyproheptadine</td>
<td>+/-</td>
</tr>
<tr>
<td>Lithium</td>
<td>1</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>THC</td>
<td>1</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Cisapride</td>
<td>1</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>Zinc</td>
<td>3</td>
<td></td>
<td>+/-</td>
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</tbody>
</table>
Fluoxetine vs. Placebo in Anorexia Nervosa

Fluoxetine
N=16

Placebo
N=17

Attia et al, 1998
Anorexia Nervosa: Fluoxetine to Prevent Relapse

Survival Distribution Function

Survival Distribution Function

Term (week)

Fluoxetine

Placebo

61%

n=27

52%

n=25

45%

n=20

42%

n=19

Log-rank chi-sq=0.11, p=0.74

Cox Model, p=0.68

(Walsh, Kaplan et al, JAMA. 295:2605-12, 2006)
Anorexia Nervosa
Olanzapine vs Placebo


\[ p = 0.03 \]
Treatment of Anorexia Nervosa
State of the Art, 2011

• For adolescents:
  – Maudsley Method

• For adults:
  – *No impressively effective, evidence-based treatment, either psychotherapy or medication*
  – Hints about possible utility of olanzapine
The Enigma of Persistence
Why is Anorexia Nervosa so difficult to treat?

- The solution to the core problem is deceptively simple: EAT!
Cognitive Neuroscience meets Anorexia Nervosa?

• The defining behavioral characteristic of Anorexia Nervosa is the avoidance of fat intake.
• This behavior can be objectively measured and is linked to clinical outcome.
• Cognitive neuroscience has learned much about the neural basis of choice.
• This knowledge can be applied to understand the neural basis of the choice to consume low-fat food in Anorexia Nervosa.

Calories consumed during Multi-Item Meals before and after weight gain
Macronutrient Composition of Test Meal

* CHO: significantly different from controls
  FAT: significantly increases in patients but remains different from controls
Outcome Status vs Pre-Discharge Diet Record

The pre-discharge diet records of the patients with better outcomes indicated:

– Greater energy density
  • Higher % of calories from fat
– Greater diet variety

**Suggesting:** the persistence of dieting behavior is a major contributor to the persistence of the illness.
Persistent Behavior

- Persistent behavior that is not innate is learned via two related but distinct processes:
  - Action-Outcome learning: goal directed
  - Stimulus-Response learning: habit formation
Action-Outcome Learning
(aka instrumental conditioning, operant conditioning)

- One learns that some action is likely to lead to a reward.
- Likelihood of doing the action is sensitive to the reward value of the outcome.
- Critical to acquisition of new behaviors.
- Key neural substrates:
  - Amygdala
  - Ventral striatum (NAc)
  - Orbitofrontal cortex

Rolls (2005): pp. 152-5,185;
Graybiel (2008)
Shohamy (2011)
Stimulus-Response Learning
(Habit Formation)

• Behavior becomes insensitive to reward value of the outcome.
• Key neural substrates:
  Dorsolateral striatum (caudate/putamen)
  Dorsolateral prefrontal cortex

Graybiel (2008)
Balleine & O’Doherty (2011)
Characteristics of Habits
(Graybiel, 2008)

Habits:

– Are learned behaviors (not innate)
– Occur repeatedly and become fixed ("overtraining")
– Once acquired, occur automatically, almost unconsciously
– Involve a structured behavioral sequence prone to be elicited by a particular context or stimulus
London
Is Dieting in Anorexia Nervosa Habitual?

• Is learned behavior (not innate):
  – Dieting is clearly learned.

• Occurs repeatedly and become fixed:
  – Repetition required to lose weight.

• Once acquired, occurs automatically, almost unconsciously:
  – No clear data, but dieting behavior occurs despite conscious desire to eat more normally.

• Involves a structured behavioral sequence prone to be elicited by a particular context or stimulus:
  – Eating behavior often involves rituals.
  – Meals, and a range of other stimuli, including negative emotion, may constitute a sufficient stimulus.
Hypothesis

The eating behaviors characteristic of individuals with Anorexia Nervosa begin as goal-directed (A-O learning) but become habitual. And, therefore, highly resistant to change. And, thereby, serve to perpetuate the disorder.
How does dieting/exercise become habitual?

• Initially (at least), it is rewarding.
  – Therefore, supports action-outcome learning.
  – Reward is intermittent and behaviors are repeated and become “over-trained.”

• Occurs during adolescence.
  – A time of bias towards reward (vs adverse outcomes).
  – A time of multiple stresses.

• Enhanced by starvation.
Preliminary, unpublished, data not shown.
Thank you!

More information:

http://columbiaeatingdisorders.org/

(including T32 post-doctoral program on Research on Eating Disorders)