Overview of Eating Disorders

Calgary Zone Mental Health Day Pre-Conference
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Jump on the Bandwagon!

16th Annual Canadian Collaborative Mental Health Care Conference

Characteristics of an Eating Disorder

1) The presence of disturbed eating behaviour

2) The presence of characteristic psychopathology

Obesity per se is not an eating disorder but is best conceptualized as a complex, heterogeneous multi-determined metabolic disturbance. However, a significant percentage of obese subjects do have disturbed eating behaviour and/or psychopathology.

Anorexia Nervosa: DSM 5 Criteria

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 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.

Prevalence of Anorexia Nervosa

DSM 5 Criteria: 1.2 %

DSM IV Criteria 0.8 %

10% of cases are males

Bulimia Nervosa: DSM 5 Criteria

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:

(1) Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time under similar circumstances

(2) A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)

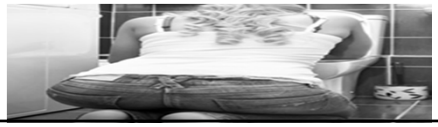
Bulimia Nervosa: DSM 5 Criteria

B. Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications, fasting; or excessive exercise.

C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once per week for 3 months.

D. Self-evaluation is unduly influenced by body shape and weight.

E. The disturbance does not occur exclusively during episodes of Anorexia Nervosa



Prevalence of Bulimia Nervosa

DSM 5 Criteria : 2.4 %

DSM IV Criteria : 1. 8%

10-15 % of cases are male

Binge Eating Disorder – DSM 5 Criteria

A. Recurrent episodes of binge eating. An episode of binge eating is:

1. Eating, in a discrete period of time an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances
2. A sense of lack of control over eating during the episode

B. The binge-eating episodes are associated the following:

1. Eating much more rapidly than normal
2. Eating until feeling uncomfortably full
3. Eating large amounts of food when not feeling physically hungry
4. Eating alone because of feeling embarrassed by how much one is eating
5. Feeling disgusted with oneself, depressed, or very guilty after overeating

Binge Eating Disorder – DSM 5 Criteria

C. Marked distress regarding binge eating is present.

D. The binge eating occurs at least once a week for 3 months.

E. The binge eating is not associated with the recurrent use of inappropriate compensatory behavior and does not occur exclusively during the course Bulimia Nervosa or Anorexia Nervosa.

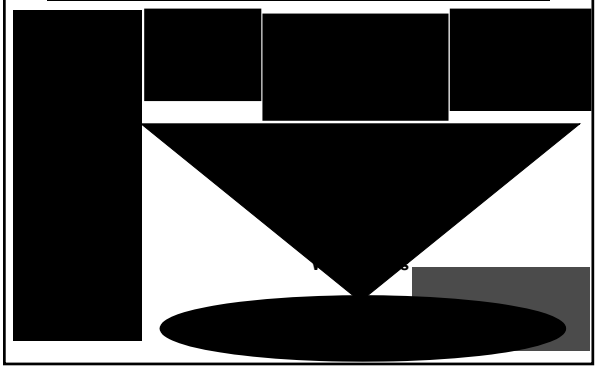
Prevalence of Binge Eating Disorder

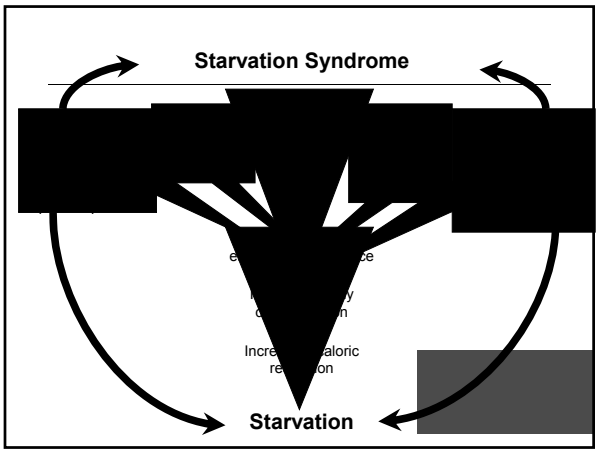
- **BED is more common than the other major eating disorders anorexia nervosa or bulimia nervosa**
- **Lifetime prevalence of ~3% among women; 2% among men in US (Hudson et al., 2007) , and ~2.0% EU (pooled WMH survey; Kessler et al., 2013)**
- **70% female, 30% male**

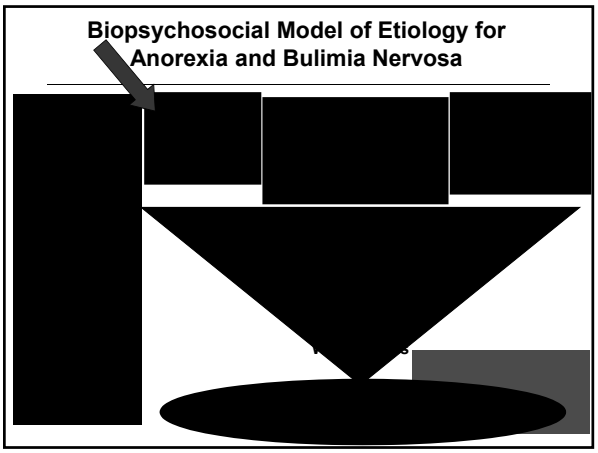
What Causes an Eating Disorder?

- **Are eating disorders due to a disturbed society?**
- **Are eating disorders due to a disturbed family?**
- **Are eating disorders due to a disturbed personality?**
- **Are eating disorders due to a disturbed mood?**
- **Are eating disorders due to a disturbed brain?**
- **Are eating disorders due to disturbed genes?**

Biopsychosocial Model of Etiology for Anorexia and Bulimia Nervosa

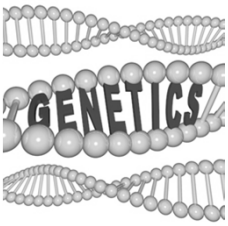


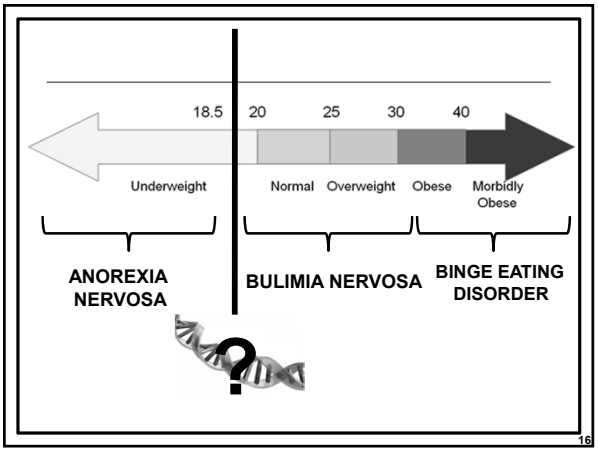




Biologic Factors

Genetics





A Range of Genetic Influence

COMPLETELY GENETIC	COMPLETELY ENVIRONMENTAL
Cystic fibrosis Huntington's Disease	Religious affiliation

Most human characteristics are partially inherited

Characteristics of Partially Inherited Disorders

- **Aggregates (clusters) in families.**

Do eating disorders run in families?

Family Studies of Eating Disorders

- Anorexia and bulimia are strongly familial
- Relatives are 7-12 times at higher risk
- Relative risk for anorexia highest
- As familial as bipolar disorder & schizophrenia
- Family studies CANNOT tell us if due to genes or environment.

Characteristics of Partially Inherited Disorders

- Aggregates in families
- MZ (identical) twin concordance is greater than DZ (non identical) twin concordance

Classical Twin Studies

- "Biological" experiment
- In a population, compare concordance of:

Monozygotic Twins

Share 100% of their genes

Dizygotic Twins

Share ~50% of their genes

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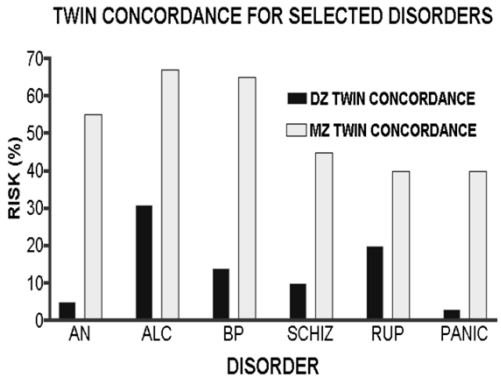
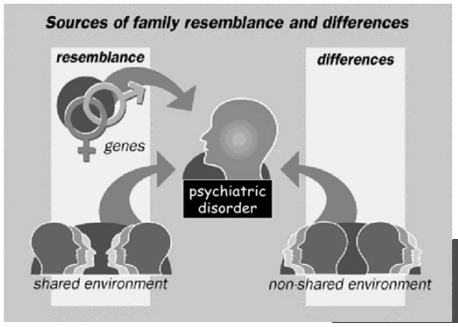


Genes or Jeans?



Quantification of Effects

(A) Additive effects of genes

- complex trait
- influenced by many genes of small/moderate effect

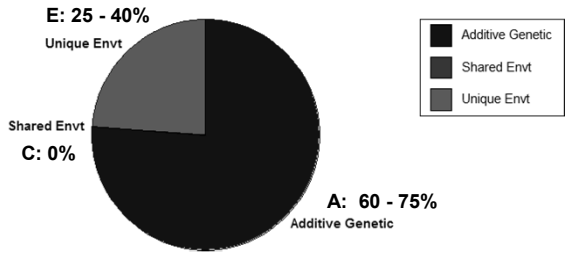
(C) "Shared" Environmental Effects

- religion
- parental rearing style
- socioeconomic status

(E) "Unique" Environmental Effects

- events experienced by one twin only

Heritability of Anorexia Nervosa



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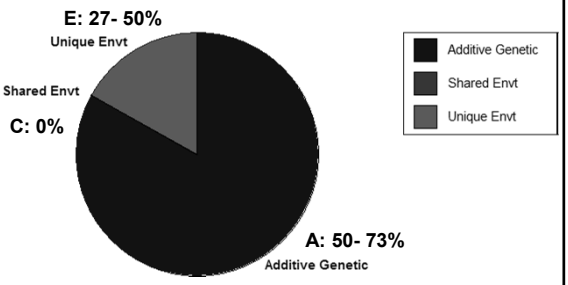
Heritability of Bulimia Nervosa



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Heritability Estimates from Twin Studies

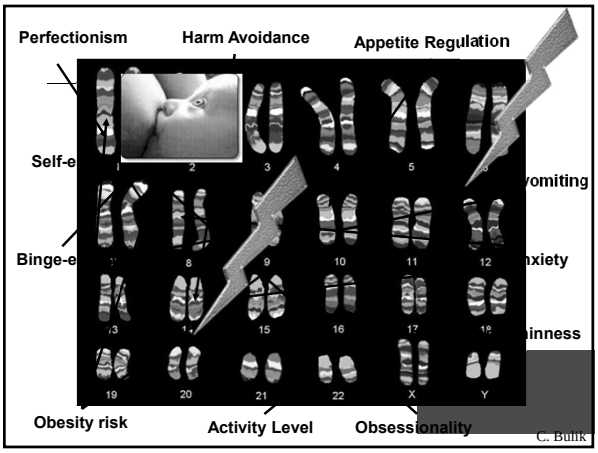
Obesity 84%
Anorexia Nervosa 70%
Schizophrenia 68%
Hypertension 57%
Alcoholism 57%
Cirrhosis 53%
Epilepsy 50%
Coronary Artery Disease 49%

What Do Twin Study Results Mean?

- 50-80% of variance in liability to eating disorders is due to additive genetic factors
- Impact of shared environment not substantial
- Both anorexia and bulimia nervosa appear to be markedly heritable

The Quest for Genes

- Human genome highly unlikely to "map on" to our diagnostic categories
- There will not be "The Anorexia Gene" or "The Depression Gene" or "The Autism Gene"
- There are multiple genetic and environmental factors of small to moderate effect operating
- Search for characteristics that underlie vulnerability



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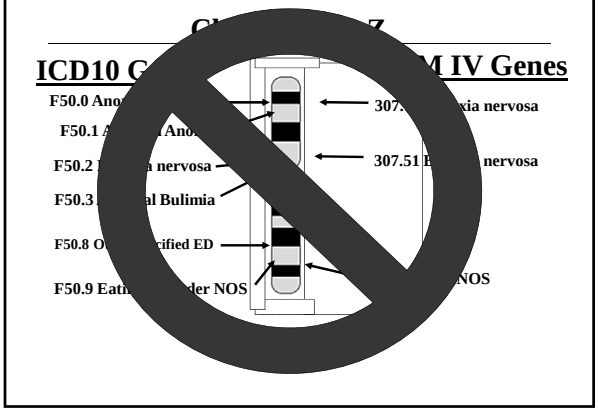


Since genes appear to be important, where are they and what to they do?

Linkage Study- Affected Sibling Pairs

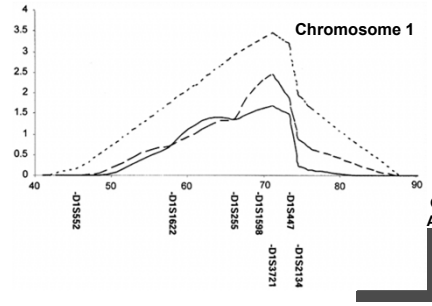
(Funded by Price Foundation 1996-2001)

- The human genome is a large place ~30,000 genes!
- Hard to know where to start to look for genes.
- Linkage allows you to narrow the search to a particular area on a particular chromosome.
- Linkage is essentially a test for deviation from what is expected to occur randomly.

Linkage Analysis With Full Sample

As expected, underwhelming...

Families Containing at Least Two Restrictor AN



Grice et al. 2002
Am J Hum Genet

Candidate genes in the area of linkage on Chromosome 1p

SNPs identified in the AN sample:

- Serotonin 1 D receptor gene
- Opiod delta receptor gene
- Dopamine D2 receptor gene

Whole Genome Wide Association Studies (GWAS) in AN

1) Welcome Trust

Goals of this study : genotyping of 4,000 cases with AN and 4,000 controls

Association analyses of SNP genotypes and CNV (copy number variations) to identify genetic variants that confer risk for AN

Results: One SNP on chr5 exceeded genome-wide significance; replication sample underway

2) Price Foundation Consortium/NIMH

Results: Evidence for role of EPHX2 GENE variants: enzyme involved in cholesterol metabolism
13q12 deletion more common in AN

3) PGc AN: To find whole genome wide significance, ongoing collection of samples; currently at 10,000

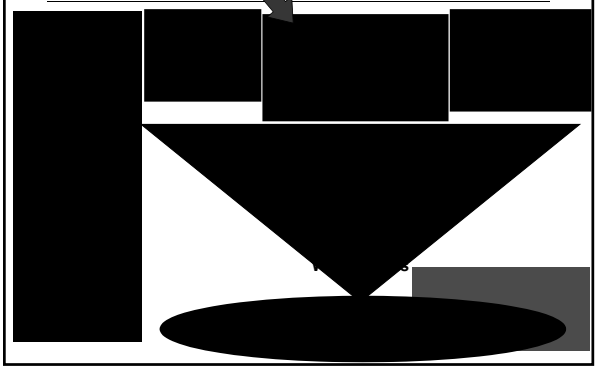
Biologic Factors

Genetics

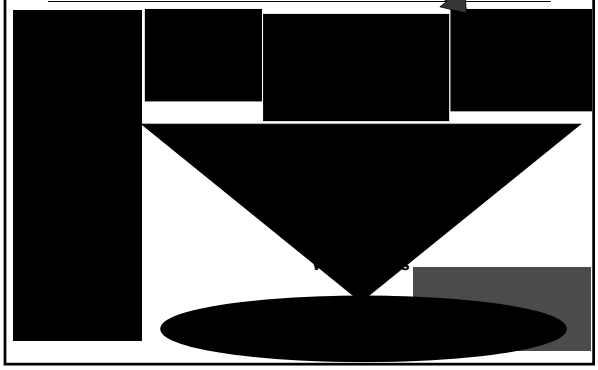
Gender :

- **Why do women develop eating disorders at 10 times the rate of men ?**
- **The brains of women are much more sensitive to dietary manipulation than are the brains of men**

Biopsychosocial Model of Etiology for Anorexia and Bulimia Nervosa



Biopsychosocial Model of Etiology for Anorexia and Bulimia Nervosa



Sociocultural Factors

1) Family

Can be protective by providing a forgiving environment or can magnify the cultural pressure for thinness and stigma against overweight/obesity

Know your child's vulnerabilities

Be mindful of activities that focus unduly on weight and shape and can potentially further damage child's self esteem :

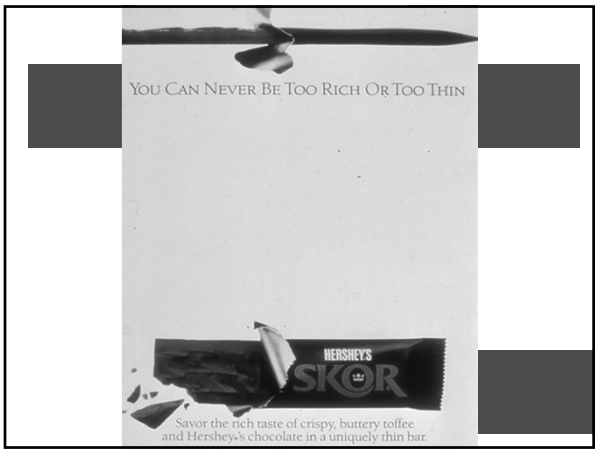
- **Gymnastics**
- **Dance (Ballet)**
- **Modeling**

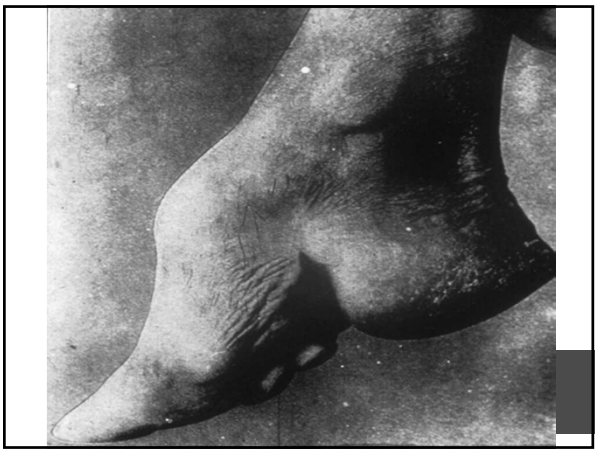
Sociocultural Factors cont . . .

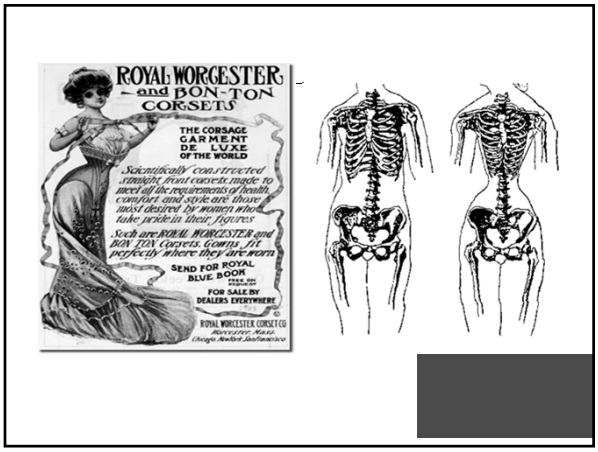
Family
Vocation / Extracurricular
- **Competitive Athletics**
- **Dance (Ballet)**
- **Modeling**

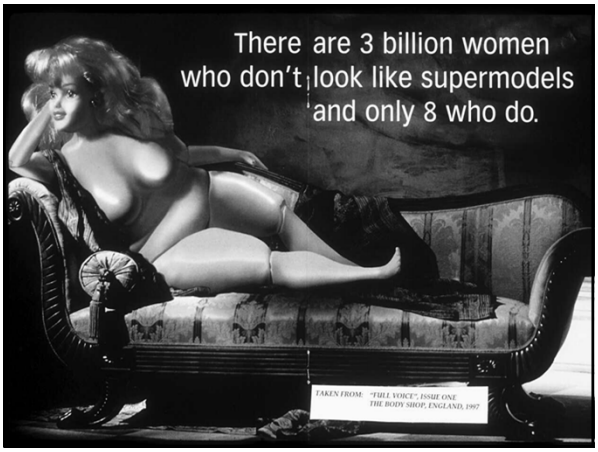
Media

The famous faces of eating disorders







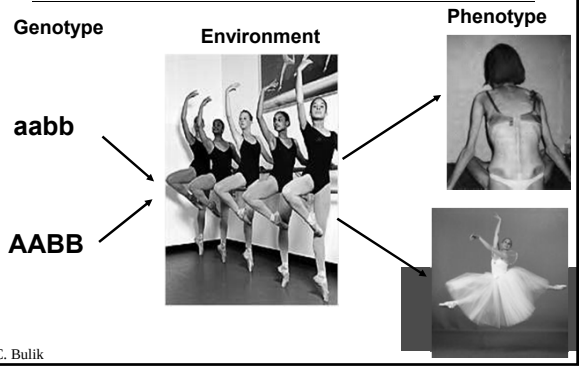


High Risk Profile: 10 year old girl

1. She has family history of eating disorder, depression, alcoholism, and obesity.
2. She is considered "chubby".
3. Her parents are overly weight and shape preoccupied.
4. Her mother is chronically depressed and turns to her for support (she is "parentified").
5. She is in a competitive ballet class and gymnastics.
6. She was molested by neighbor's son while babysitting her.

Teasing Out Genetic and Environmental Effects

Gene X Environment Interaction



C. Bulik

Where Do We Stand? What Are Our Responsibilities?

We need to:

- Debunk the myth of a purely societal cause of eating disorders
- Emphasize that genes or environment ALONE will not suffice to cause eating or other psychiatric disorders
- Translate scientific knowledge into practice
- Convey accurate information to the public
- Provide protective environments to minimize effects of genetic risks

Protective Environments

- We hope that appropriate parenting can protect against gene expression
- Modeling healthy eating
- Modeling healthy self-esteem (not body based)
- Early detection of symptoms and provide early intervention
- Parenting training for moms with eating disorders

"GENES LOAD THE GUN, THE ENVIRONMENT PULLS THE TRIGGER"

General Principles of Treatment

1. Reverse starvation syndrome
   a) nutritional rehabilitation through
      provision of adequate amount of calories
      - Solid food
      - liquid supplementation
      - tube feeding (rare)
   b) weight gain
2. Treat target symptoms
   a) binge eating
   b) purging
   c) exercising

General Principles of Treatment cont . . .

3. Treat comorbidity
   a) Depression
   b) Anxiety
   c) Substance abuse
   d) Medical complications
4. Treat underlying psychosocial issues
   a) Individual
   b) Family

Treatment of Anorexia Nervosa

"The treatment required is obviously that which is fitted for persons of unsound mind. The patients should be fed at regular intervals, and surrounded by persons who would have moral control over them; relations and friends being generally the worst attendants . . . I do not at present prescribe medicines, because the nursing and the food are more important than anything else."

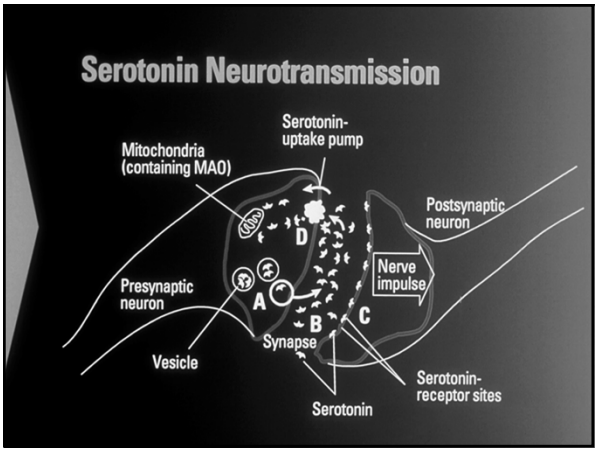
William Gull, 1874

Drug Treatment of Anorexia Nervosa (AN)

Goals of Pharmacotherapy in AN:

- **Efficacy in promoting weight restoration**
- **Efficacy in promoting weight maintenance**
- **Efficacy in treating the core disturbances in AN: cognition, affect (depression and anxiety), activity**
- **Efficacy in treating comorbid psychopathology**
- **Tolerability and safety**

Why are SSRI's ineffective in AN?



What about antidepressant treatment for weight restored patients with AN ?

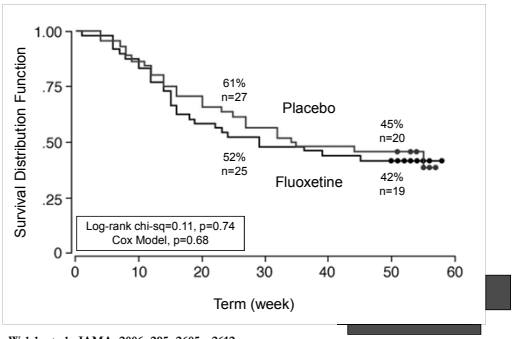
Fluoxetine after weight restoration in anorexia nervosa : A randomized placebo controlled trial

(JAMA et al 2006)

***A*llan *S. K*aplan, MD, FRCP(C)**
Toronto

B Timothy Walsh MD
New York

Fluoxetine vs Placebo
Dropout = Relapse



Walsh et al., JAMA. 2006; 295: 2605 - 2612

Current Treatment for Anorexia Nervosa

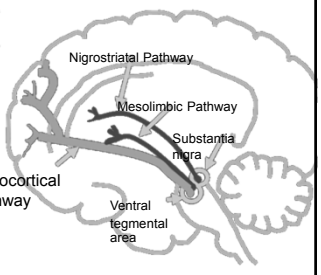
There are currently no established evidence based drug treatments for acutely ill underweight patients with AN. There are currently no evidence based psychotherapies for adults with anorexia nervosa. We need to think "out of the box" and develop innovative approaches

Dopamine Neurotransmission

Dopamine

Anorexics have disturbances in:

cognition (aberrant salience)
activity (hyperactivity)
anhedonia (lack of pleasure)
mood (dysphoric)



Atypical Antipsychotic Treatment of Anorexia Nervosa

NIMH R21 MH 69868

Randomized, Double-Blind, Placebo-Controlled Trial of Olanzapine in Anorexia Nervosa*

Allan S. Kaplan MD FRCP(C)
University of Toronto

Evelyn Attia MD
Columbia University

*** Attia E. Kaplan A et al. Olanzapine versus placebo for out-patients with anorexia nervosa. Psychological Medicine 2011 Oct;41(10):2177-82**

Weight change during study participation

	Total	Olanzapine (N=11)	Placebo (N=12)	p
Total weight gained for randomized patients during study participation (pounds)	**3.90 ± 5.74**	**8.14 ± 6.42**	**1.80 ± 4.30**	**t(21) = -1.9, (p =.047)**
Weekly weight gained (pounds/week)	**0.44 ± 1.10**	**1.05 ± 0.91**	**0.01 ± 1.10**	**t(21) = -2.1, (p =.045)**

A Meta-Analytic Study Evaluating Brain Activation in Anorexia Nervosa

Allan S Kaplan ,Kate Strasburg, Paul B. Fitzgerald, Angela R. Laird, Jerome Maller, Zafiris J. Daskalakis,

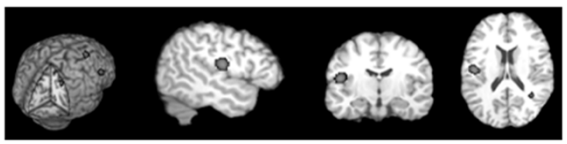
p = 0.038

minALE = 1.12 x 10^{-4}

maxALE = 0.007

Region	BA	Volume (mm^3)	Weighted Centre (x, y, z)	Max ALE Value
L frontal lobe, L medial frontal gyrus	6	2296	-18, 4, 52	0.007
R occipital lobe, R lingual gyrus	18	1464	18, -72, 2	0.007
L insula	13	1264	-46, -16, 14	0.006

Significantly *increased* activation in the insular region(following exposure to *emotionally aversive stimuli* in AN patients compared to controls. **rTMS targeting the insula ?**

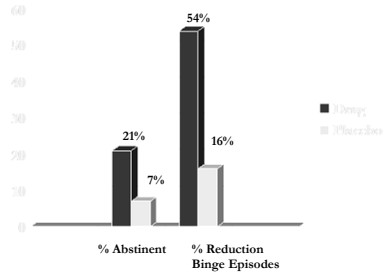


Drug Treatment of Bulimia Nervosa (BN)

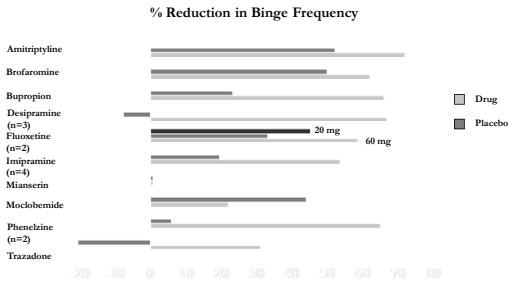
Goals of Pharmacotherapy in BN

- Efficacy in reducing binge eating/purging
- Efficacy in maintaining abstinence from binge eating /purging
- Efficacy in treating the core disturbances in BN: affect regulation, self esteem, impulsivity
- Efficacy in treating comorbid psychopathology
- Tolerability and safety

Antidepressant Treatment of BN
Randomized Placebo Controlled Trials (n=21)



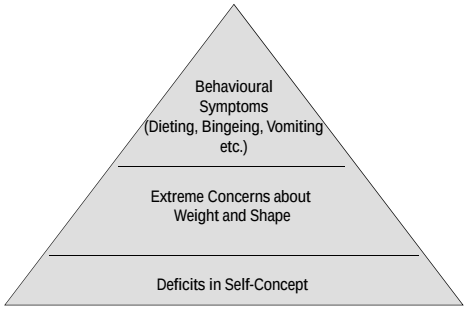
Antidepressant Treatment of BN
Randomized Placebo Controlled Trials (n=17*)



* Binge data NA for Blouin et al 1988, Kennedy et al 1988, Romano et al 1988, Milano et al 2004

Psychological Treatments for Bulimia Nervosa and Binge Eating Disorder

The CB Model Of Eating Disorders



Cognitive Behavior Therapy for Binge Eating Disorder ~ 3 Phases

Phase I focuses on normalizing eating behavior

- Self-monitoring for food intake, including binge episodes.
- Self-monitoring of thoughts and feelings associated with dysregulated eating.
- Specific interventions designed to normalize eating behaviour

Cognitive Behavior Therapy for Binge Eating Disorder ~ 3 Phases

Phase II focuses on dysfunctional thinking

- **Cognitive restructuring directed at dysfunctional thoughts that are related to the development and maintenance of the eating disorder.**

Cognitive Behavior Therapy for Binge Eating Disorder~ 3 Phases

Phase III focuses on relapse prevention

- **Strategies to consolidate and facilitate maintenance of changes after treatment ends.**

CBT and Antidepressant Pharmacotherapy for Bulimia Nervosa

1. **Considering all studies together, short-term CBT lead to a reduction in bulimic symptoms of approximately 85% and a remission rate of approximately 55%.**
2. **Considering all studies together, pharmacotherapy lead to a 56% reduction in symptoms and a 25 % remission rate.**

CBT and Antidepressant Pharmacotherapy for Bulimia Nervosa

3. **In studies directly comparing antidepressants to CBT, there tends to be a better outcome with CBT than pharmacotherapy . CBT was much more acceptable than antidepressants.**
4. **In studies examining antidepressants alone or CBT alone compared to a combination of antidepressants and CBT, there are greater rates of remission in patients treated with combination therapy than either alone.**

Drug Treatment of Binge Eating Disorder

Goals of Pharmacotherapy in BED

- **Efficacy in reducing binge eating**
- **Efficacy in maintaining abstinence from binge eating**
- **Efficacy in treating comorbid psychopathology, including weight loss/ obesity**
- **Efficacy in treating the core disturbances in BED: affect regulation, self esteem, impulsivity**
- **Tolerability and safety**

Current Status: Pharmacologic Treatments for Binge Eating Disorder

1. **The first drug approved by the FDA for BED, in January 2015, is lisdexamfetamine (Vyvanse)**
2. **RCTs for other classes of drugs are characterized by small samples, brief treatment and no long term follow**
3. **Overall, pooling all studies other than LDX, approximately 45 % of subjects receiving medication achieved 100 % remission from binge eating compared to 28% on placebo**
4. **Across all studies, mean weight loss was 3.4 kg greater on drug vs placebo, with SSRI < antiepileptic< antiobesity drugs**
5. **Anticonvulsants (Topiramate) is effective in reducing binge eating and inducing weight loss but limited by SEs**
6. **Obesity drugs- Orlistat – limited by side effects; Sibutramine/fenfluramine - removed from market because of cardiac complications**
7. **No apparent advantage of drug added to CBT**
8. **No published trials of maintenance therapy**

Psychostimulants: New Pharmacologic Treatment for Binge Eating Disorder

High rates of comorbidity of BED and ADHD:

- Obesity, BED, and ADHD commonly co-occur (30%) , and symptoms of ADHD have been proposed to contribute to the disinhibited eating characterizing binge eating and weight gain
- BED and ADHD are both characterized by dopamine deficiency and heightened reward sensitivity (" reward deficiency syndrome" and deficient tonic DA signalling) as well as impulsivity, both of which are associated with overeating
- Psychostimulant medications , utilized to manage ADHD, target the dopamine system, and have been associated with increased behavioural regulation and decreased appetite and weight

Lisdexamfetamine (Vyvanse) in the Treatment of BED (McElroy et al 2015)*

- Multicenter, randomized, double blind, parallel group, forced dose(30mg, 50mg, 70mg/day) titration, placebo controlled clinical trial
- 30 sites, 255 subjects with BED treated for 11 weeks; 3weeks titration and 8 weeks maintenance
- Exclusion criteria: any comorbid psychiatric condition
- Efficacy - change from baseline to endpoint in number of binge days/week
- Results: The 50- and 70-mg/d treatment groups demonstrated significantly greater efficacy compared with the placebo group in decreasing number of BE days, BE cessation, and global improvement.

* JAMA Psychiatry 2015 :72 : 235-246

RCT of Long Acting Methylphenidate Compared to CBT in the Treatment of BE

Quilty L, PI; Kaplan A, Davis Co-I's; Ontario Mental Health FD)

Aim: To evaluate the therapeutic effect of long acting methylphenidate compared to CBT in patients with BED.

Hypotheses:

- Subjects who are randomized to receive long acting methylphenidate will demonstrate significant decrease in binge eating episode frequency and BED severity
- Pre-treatment ADHD symptom severity will be associated with a preferential treatment response to medication as compared to CBT
- Pre-treatment depression symptom severity will be associated with a preferential treatment response to CBT as compared to medication

RCT of Long Acting Methylphenidate Compared to CBT in the Treatment of BED

Protocol:

CBT treatment:
Participants randomly assigned to receive individual CBT will attend 16 50-minute appointments over the course of 12 weeks

Medication :
Participants randomly assigned to receive long acting methylphenidate will attend weekly appointments with study psychiatrists for the first four weeks, and then biweekly appointments for the last eight weeks.

Dosage: 18 mg/day, to be increased to 36 mg/day at week 2, 54 mg/day at week 3, and 72 mg/day at week 4. Dosage levels may be maintained or decreased to manage medication side effects.

RCT of Long Acting Methylphenidate Compared to CBT in the Treatment of BED

Inclusion criteria:

1. DSM-5 criteria for BED
2. Binge episodes at least three days per week during the past two weeks
3. BMI ≥ 25
4. 18 to 50 years of age
5. Fluent in reading English
6. Capacity to give informed consent

RCT of Long Acting Methylphenidate Compared to CBT in the Treatment of BED

Exclusion criteria:

1. Pregnancy or lactation
2. Psychotherapy or behavioural treatment for eating or weight initiated during the past three months
3. Psychotropic medications during past 4 weeks or use of psychostimulants to manage eating or weight past 6 months
4. Current mania, psychosis, substance dependence, or dementia
5. Current severe suicidality or homicidality
6. Current medical conditions that affect weight or BED symptoms or are contraindicated for methylphenidate such as diabetes or thyroid disease
7. Carrdiac illness such as myocardial infarction or stroke during the past six months
8. History of seizures
9. Uncontrolled hypertension (>160/100), tachycardia (heart rate > 110), arrhythmias or conduction abnormalities
10. Current medications that affect weight

Long Acting Methylphenidate in BED: Preliminary Results

Participants:

- ***N* = 16 females randomized to drug, age 18-55 years (*M* = 28.44; *SD* = 7.64)**
- **DSM-5 diagnosis of BED**
- **50% met criteria for a comorbid condition**
  - **Mood Disorders: MDD: *n* = 1; Dysthymic Disorder: *n* = 1; Depressive Disorder NOS: *n* = 1**
  - **Anxiety Disorders: Social Phobia = 1; PTSD: *n* = 1; GAD: *n* = 1**

Long Acting Methylphenidate in BED: Preliminary Results

1. BMI and Weight at Week 0, 6, and 12:

	Week 0 (*n*=16) *M* (*SD*)	Week 6 (*n*=9) *M* (*SD*)	t	p	*d*	Week 12 (*n*=7) *M* (*SD*)	t	p	d
BMI	36.56 (6.70)	34.49 (6.40)	.75	*ns*	.33	28.31 (6.70)	1.89	.07	.9
Weight (lbs)	221.25 (40.91)	209.22 (34.47)	.74	*ns*	.32	198.86 (82.69)	2.06	.05	.98

2. Binge Frequency at Week 0, 6, and 12:

	Week 0 *n*=15 *M* (*SD*)	Week 6 *n*=9 *M* (*SD*)	*t*	*p*	*d*	Week 12 *n*=7 *M* (*SD*)	*t*	*p*	*d*
Binge/Week	19.13 (11.67)	5.44 (9.11)	3.00	<.01	1.32	3 (3.74)	3.53	<.01	1.7

Conclusions

1. **The eating disorders Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorder are multidetermined.**
2. **A risk factor model best explains the etiology of these conditions.**
3. **The prevention of psychological and sociocultural risk factors should be a high priority for schools, parents and health-care providers.**

Conclusions cont . . .

4. Early identification of cases is critical to maximize recovery and prevent chronicity.

5. Bulimia nervosa and Binge Eating Disorder are more responsive to treatment and have a better outcome than Anorexia Nervosa (70-80% recovery rate for BN/BED vs. 40% for AN)

Questions/ Discussion ????