Psychopharmacology of Eating Disorders

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Pre-Lecture Questions Follow
1. The following agent has been demonstrated to be effective in the treatment of anorexia nervosa.

a. Olanzapine  
b. Fluoxetine  
c. Imipramine  
d. None of the above
2. The following class(es) has/have convincing data from placebo-controlled trials supporting its/their utility in the treatment of bulimia nervosa.

a. Anticonvulsants
b. Antipsychotics
c. Antidepressants
d. All of the above
e. None of the above
3. The dose of fluoxetine established to be most effective in the treatment of bulimia nervosa is:

a. 10 mg/d
b. 20 mg/d
c. 40 mg/d
d. 60 mg/d
e. 80 mg/d
4. In controlled trials, at least one-half of the anti-bulimic effect of fluoxetine is apparent within (choose the shortest correct answer):

a. 5 days  
b. 2 weeks  
c. 6 weeks  
d. 3 months  
e. 6 months
5. The following class(es) has/have data from placebo-controlled trials supporting its/their utility in the treatment of binge eating disorder:

a. Anticonvulsants (e.g. topiramate)
b. Weight loss agents (e.g. sibutramine)
c. Antidepressants
d. All of the above
e. None of the above
Outline: Psychopharmacology of Eating Disorders

I. Anorexia Nervosa
   A. Many agents suggested as useful, but few examined in controlled trials
   B. Characteristics of patients in controlled trials
   C. Rationale for agents examined
   D. Results of controlled trials of underweight patients
   E. Results of controlled trials of weight-restored patients
   F. Summary
I. Bulimia Nervosa
   A. A number of agents have been examined in controlled trials, but, by far, most of the data relate to antidepressants
   B. Characteristics of patients in controlled trials
   C. Rationale for antidepressants
   D. Results of controlled antidepressant trials
   E. Results of trials of other agents
   F. Summary
I. Binge Eating Disorder
   A. Diagnostic and clinical features
   B. Goals of treatment (threefold)
   C. Agents examined
   D. Results of controlled trials: binge frequency and weight
   E. Summary
**Major Teaching Points:**

**Psychopharmacology of Eating Disorders**

**Anorexia Nervosa:**
No medication of proven utility!
Calories and psychotherapy are the best established interventions.

**Bulimia Nervosa:**
First line medication: SSRI’s (fluoxetine).
Second line medication: SNRI? Topiramate?

**Binge Eating Disorder:**
Many interventions appear helpful, but best approach is uncertain at present.
Psychopharmacology of Eating Disorders

Three syndromes to be considered:

• Anorexia Nervosa
• Bulimia Nervosa
• Binge Eating Disorder
Anorexia Nervosa

Among the interventions proposed in the literature as being effective are the following somatic treatments:

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

*Is any of this the ‘Right Stuff’?*

The only way to know is via placebo-controlled trials.
Psychopharmacology of Anorexia Nervosa
Clinical Characteristics

- Patients in studies are:
  - underweight
    *(required by diagnostic criteria)*
  - usually hospitalized
    *(in real world, most patients are outpatients)*
  - usually adults
    *(though the illness usually starts in adolescence, most patients presenting for treatment are over 18)*
Psychopharmacology of Anorexia Nervosa
Rationale for Agents Examined

- Take advantage of side effects
  Weight gain
- Or, treat symptoms which are often prominent in Anorexia Nervosa
  Psychotic-like thinking about weight
  Depression
  OCD
Anorexia Nervosa: Controlled Trials Conducted

- Antipsychotics
- Antidepressants
- 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>
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<tr>
<td>Antipsychotic</td>
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<td>CMI, AMI (2), FLX</td>
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<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>
</tr>
</tbody>
</table>

* '-' indicates no better than placebo
  ' +/- ' indicates small, clinically unimpressive effects
Anorexia Nervosa
Controlled Trial of Fluoxetine

The next two slides illustrate the general pattern of medication trials of anorexia nervosa.

The first slide shows increase in weight; the second shows decrease in depression (assessed by the Beck Depression Inventory).

This is the only controlled trial of an SSRI in underweight patients with anorexia nervosa.
Fluoxetine vs. Placebo in Anorexia Nervosa

Fluoxetine
N=16

Placebo
N=17

Attia et al, 1998
Fluoxetine vs. Placebo in Anorexia Nervosa

Attia et al, 1998
Anorexia Nervosa: Summary of Controlled Trials in Underweight Patients

• Only a very small number of trials.
• But, *no* evidence of utility of any agent.
• One hypothesis to explain this ineffectiveness has been that malnutrition causes neurochemical changes that interfere with actions of medications.
• Therefore, studies have begun to examine the utility of medications in preventing relapse among patients who have recently regained weight.
Anorexia Nervosa: SSRI’s for Relapse Prevention

- Kaye et al (2001)
  Small study: 35 weight-restored, non-binge eating patients
  Fluoxetine vs Placebo
  Lower relapse rate on fluoxetine

  93 weight-restored patients, all receiving CBT
  Fluoxetine vs Placebo
  No evidence of benefit (see next slide)
Fluoxetine vs Placebo
Dropout = Relapse

Survival Distribution Function

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
Psychopharmacology of Anorexia Nervosa
New Ideas

Olanzapine

4 open trials reported.
Some patients gain weight, but many are unwilling to take it or to remain on it.
Placebo-controlled data needed.
Psychopharmacology of Anorexia Nervosa Summary

• No medication clearly effective, either for underweight patients or to reduce relapse among patients following weight gain.

• Rumors of utility of olanzapine – more data needed.

• Best biological treatment is calories!
Bulimia Nervosa

Controlled trials have been conducted of the following agents:

- Anticonvulsants
- Lithium
- Fenfluramine
- Antidepressants
- 5-HT3 antagonist (ondansetron)
- Topiramate

By far, antidepressants are the most studied, and have most convincing evidence of efficacy. Therefore, will focus on that class.
Psychopharmacology of Bulimia Nervosa

Clinical Characteristics

• Patients in studies usually:
  
  use vomiting to compensate
  *(DSM-IV allows other methods)*

  are of normal weight

  are almost all female

  are young adults
Bulimia Nervosa
Rationale for Antidepressants

- Comorbidity with depression
- Role of serotonin in satiety
## Controlled Trials of Antidepressants in Bulimia Nervosa

<table>
<thead>
<tr>
<th>Author</th>
<th>Medication</th>
<th>n</th>
<th>Length (wks)</th>
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<tr>
<td>Sabine et al</td>
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<td>Phenelzine</td>
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<td>Agras et al</td>
<td>Imipramine</td>
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<td>Barlow et al</td>
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<td>Desipramine</td>
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<td>Horne et al</td>
<td>Bupropion</td>
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<td>Pope et al</td>
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<td>Mitchell et al</td>
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<td>Kennedy et al</td>
<td>Brofaromine</td>
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<td>Alger et al</td>
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<tr>
<td>Schmidt et al</td>
<td>Fluvoxamine</td>
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<td>Milano et al</td>
<td>Fluvoxamine</td>
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<tr>
<td>Milano et al</td>
<td>Sertraline</td>
<td>20</td>
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Antidepressant Treatment of Bulimia Nervosa

% Reduction in binge frequency

-40 -20 0 20 40 60 80 100

IMI*
AMI
DMI*
IMI*
Bupropion*
Phenelzine*
Trazodone*
IMI*
Fluoxetine*
DMI*
Fluoxetine*
Brofaromine
IMI
Fluvoxamine
Fluvoxamine*
Sertraline*

active med
placebo

20 mg/d
60 mg/d
Fluoxetine, at 60 mg/d, was initiated on Day 1. Note rapidity of response! Was well-tolerated.
Notes on Previous Slides

- Much variability in placebo response, and no head-to-head trials of different medications.
- In virtually all trials, antidepressant treatment is associated with greater improvement than placebo.
- Fluoxetine (60 mg/d) is superior to placebo; 20 mg/d is not.
- Fluoxetine is only SSRI with substantial evidence of efficacy, and only medication FDA-approved for bulimia.
Bulimia Nervosa: Concerns re Antidepressant Treatment

- Psychotherapy works at least as well.
- Single course of a single drug only rarely produces complete remission of symptoms.
- Side effects, etc.

**So, psychotherapy (CBT) usually first-choice treatment**

- There is some evidence that adding medication to psychotherapy is beneficial, but only modestly.
Psychopharmacology of Bulimia Nervosa
Other Ideas

Ondansetron
Topiramate
Ondansetron vs Placebo
Faris et al, 2000

- 5HT3 antagonist
- Effective anti-emetic
- A single small study indicates efficacy versus placebo in patients with refractory BN
Topiramate for Bulimia Nervosa

- Topiramate
  - Effective anti-epileptic.
  - Appears effective in obesity.
  - Two placebo controlled trials support efficacy.
  - Side effects (e.g., cognitive slowing, paresthesias, kidney stones) potentially problematic.
Psychopharmacology of Bulimia Nervosa

Summary

• Antidepressants reduce symptoms
• Fluoxetine is only SSRI extensively studied well tolerated at 60 mg/day
• CBT also clearly effective combine treatments? sequence treatments?
• Experimental ondansetron, topiramate
Binge Eating Disorder: Key Diagnostic Features

- Recurrent binge eating (objectively large amount of food and loss of control) *(same as bulimia)*
- No compensatory behavior *(clearly different from bulimia)*
- Marked distress about the behavior

Binge Eating Disorder
Clinical Features

Compared with patients with anorexia nervosa and bulimia nervosa, those with Binge Eating Disorders:

- are older (~middle aged)
- more frequently male (40-50%)

Most are overweight or obese.

Low levels of mood and anxiety disturbance are common.
Goals of Treatment for Obese Patients With BED

• Normalization of eating patterns and cessation of binge eating (BEHAVIORAL)
• Management of obesity (SOMATIC)
• Reduction of overall distress: remediation of depressive symptoms and enhanced self-acceptance (PSYCHOLOGIC)
Medications Examined for Treatment of BED

- **Antidepressants**
  - TCAs: desipramine, imipramine
  - SRIs: fluvoxamine, sertraline, fluoxetine, citalopram

- **FDA approved antiobesity agents**
  - sibutramine
  - orlistat

- **Other**
  - Naltrexone
  - Topiramate
## Controlled Medication Trials in BED

<table>
<thead>
<tr>
<th>Author</th>
<th>Medication(s)</th>
<th>N</th>
<th>Length (weeks)</th>
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<tr>
<td>McCann (1990)</td>
<td>Desipramine</td>
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<td></td>
<td>Naltrexone</td>
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<td>Hudson (1998)</td>
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<td>McElroy (2000)</td>
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<td>McElroy (2003)</td>
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<td>Appolinario (2003)</td>
<td>Sibutramine</td>
<td>60</td>
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<td>Grilo (2005)</td>
<td>Orlistat + CBT</td>
<td>50</td>
<td>12</td>
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<tr>
<td>Golay (2005)</td>
<td>Orlistat</td>
<td>89</td>
<td>24</td>
</tr>
</tbody>
</table>

*Removed from the market.
Efficacy of Medication for Treatment of BED

% Reduction in Binge Frequency

-50 0 50 100

McCann (1990)
Alger (1991)
Stunkard (1996)
Hudson (1998)
McElroy (2000)
Arnold (2002)
Appolinario (2003)
Grilo (2005)
Golay (2005)

placebo

Desipramine  Naltrexone  Imipramine
d-Fenfluramine  Fluvoxamine  Sertraline
Fluoxetine  Citalopram  Topiramate
Sibutramine  Orlistat + CBT  Orlistat
Efficacy of Medication for Treatment of BED

Weight Loss (kg)

Alger (1991)
Stunkard (1996)
Hudson (1998)
McElroy (2000)
Arnold (2002)
Grilo (2005)
Golay (2005)
McCann (1990)
Desipramine
Fluvoxamine
Fluoxetine
Citalopram
Topiramate
Sibutramine
Orlistat + CBT
Orlistat
Conclusions: Treatment of Binge Eating Disorder

A range of treatments appear effective in reducing binge eating frequency and improving symptoms of mood disturbance.

Several forms of psychological treatment are effective. Antidepressants are effective.

The most effective interventions to aid weight loss appear to be interventions effective for obesity, in general:

- sibutramine
- orlistat
- topiramate

A significant problems in evaluating these data is the high rate of symptomatic improvement in response to non-specific interventions (i.e., a high placebo response).
Psychopharmacology of Eating Disorders

Summary

• **Anorexia Nervosa**
  
  No medication of proven utility!
  Calories and psychotherapy.

• **Bulimia Nervosa**

  First line: SSRI’s (fluoxetine).
  Second line: SNRI? Topiramate?

• **Binge Eating Disorder**

  Many interventions appear helpful, but best approach is uncertain at present.
Available at NYSPI/Columbia are:

free treatment for research participants: Anorexia Nervosa, Bulimia Nervosa, Binge Eating

post-graduate fellowship opportunities

www.eatingdisordersclinic.org
Post-Lecture Questions Follow
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a. Anticonvulsants (e.g. topiramate)
b. Weight loss agents (e.g. sibutramine)
c. Antidepressants
d. All of the above
e. None of the above
Answers:

1) d
2) c
3) d
4) b
5) d