Psychopharmacology of Eating Disorders

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Pre-Lecture Questions Follow

1. The following agent has been clearly 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

II. 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

III. 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

Anorexia nervosa:

- No medication of proven utility!
- Recent interest in olanzapine, but very limited data.
- 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 studies of medication have focused on patients 18 yo or older)

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

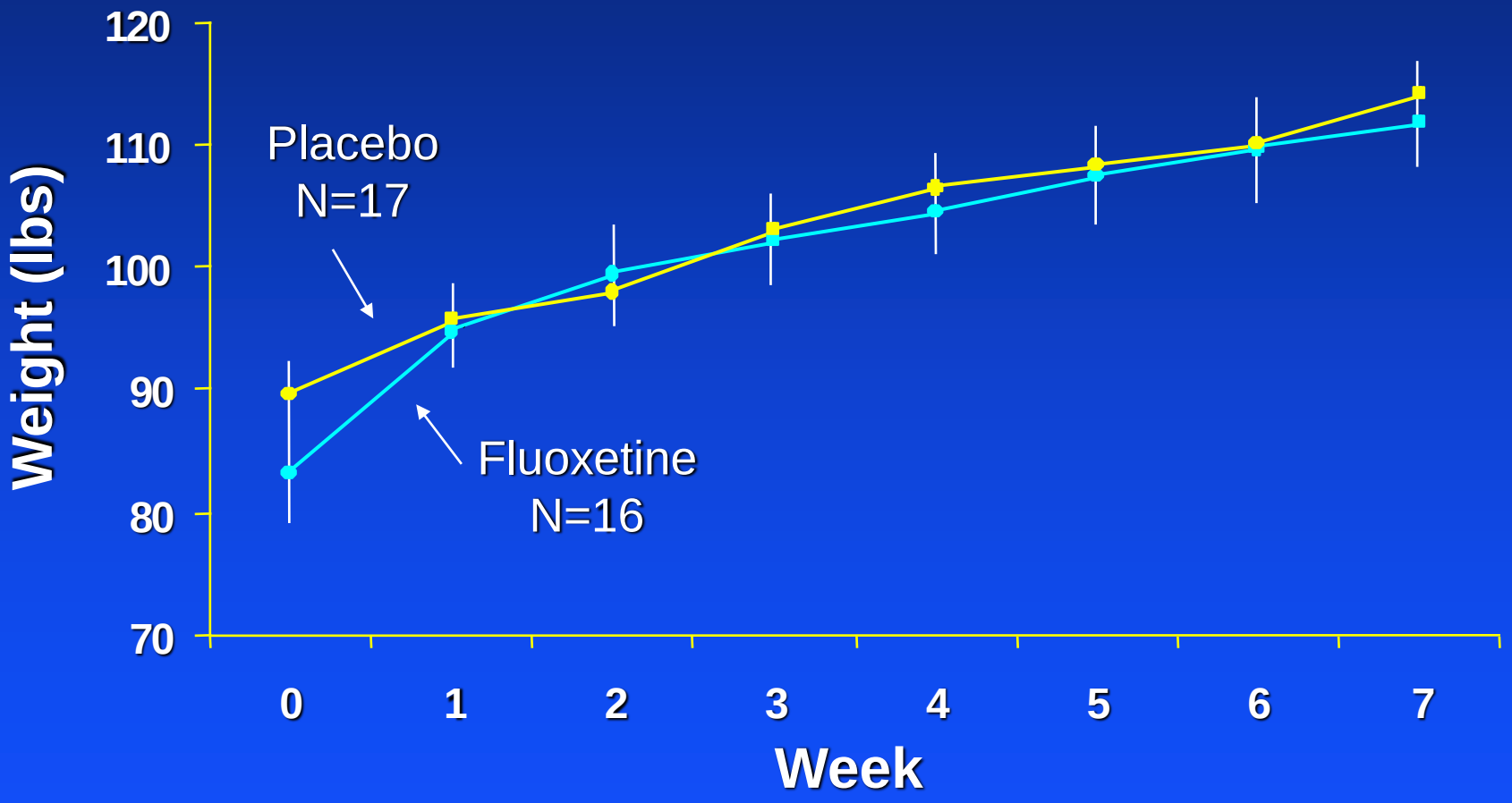
Anorexia Nervosa: Controlled Trials

Class	# Trials	Medication	Results
Antidepressant	4	CMI, AMI (2), FLX	-
Antipsychotic	2	Sulpiride, Pimozide	-
	1	Olanzapine	+
Serotonin Antagonist	3	Cyproheptadine	+/-
Lithium	1		-
THC	1		-
Cisapride	1		+/-
Zinc	3		+/-

Anorexia Nervosa
Controlled Trial of Fluoxetine

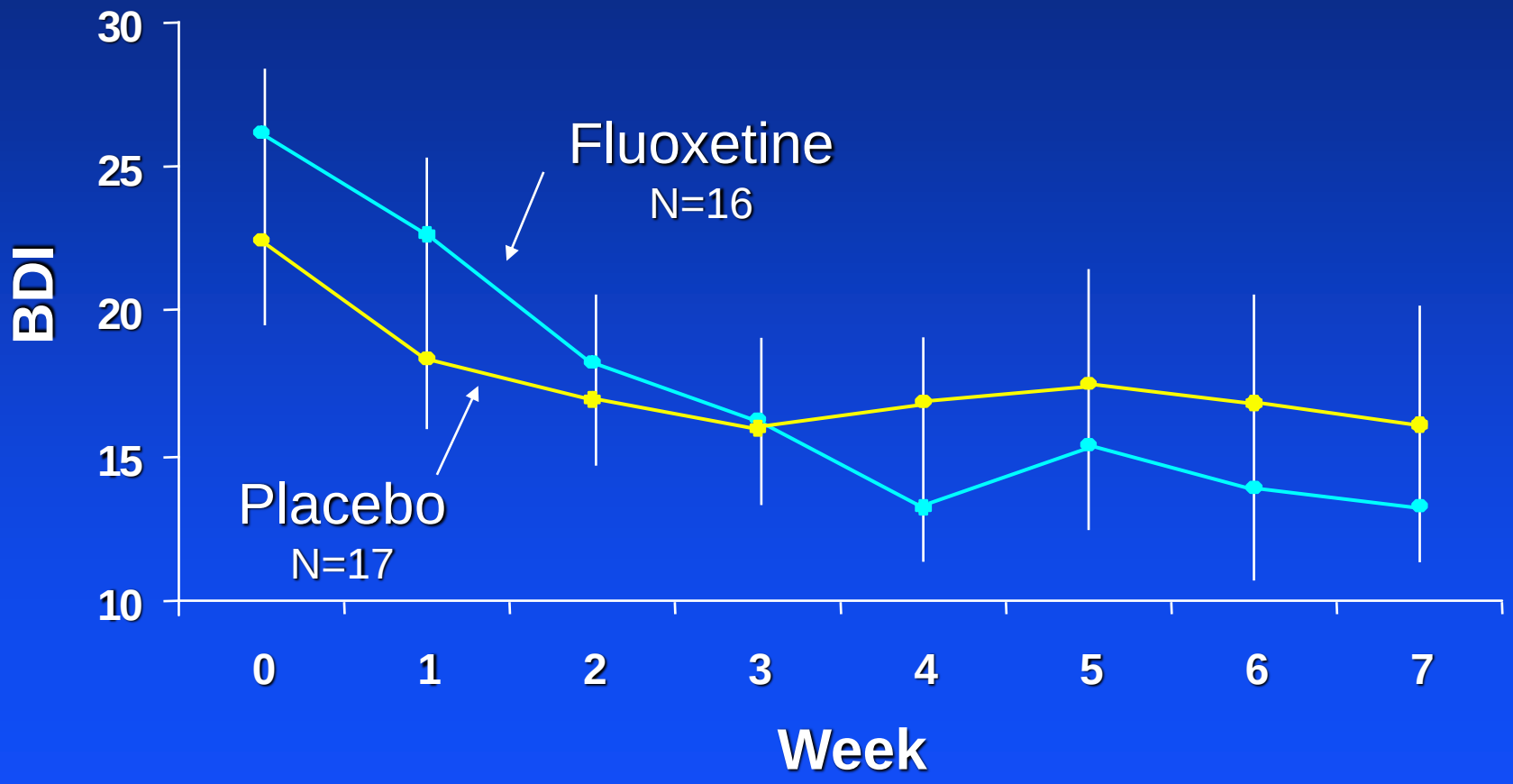
- **The next two slides illustrate the general pattern of medication trials of anorexia nervosa.**
  - **The first slide shows increase in weight; the second shows decrease in depression (assessed by the Beck Depression Inventory).**
- **This is the *only* controlled trial of an SSRI in underweight patients with anorexia nervosa.**

Fluoxetine vs. Placebo in Anorexia Nervosa



Attia et al, 1998

Fluoxetine vs. Placebo in Anorexia Nervosa



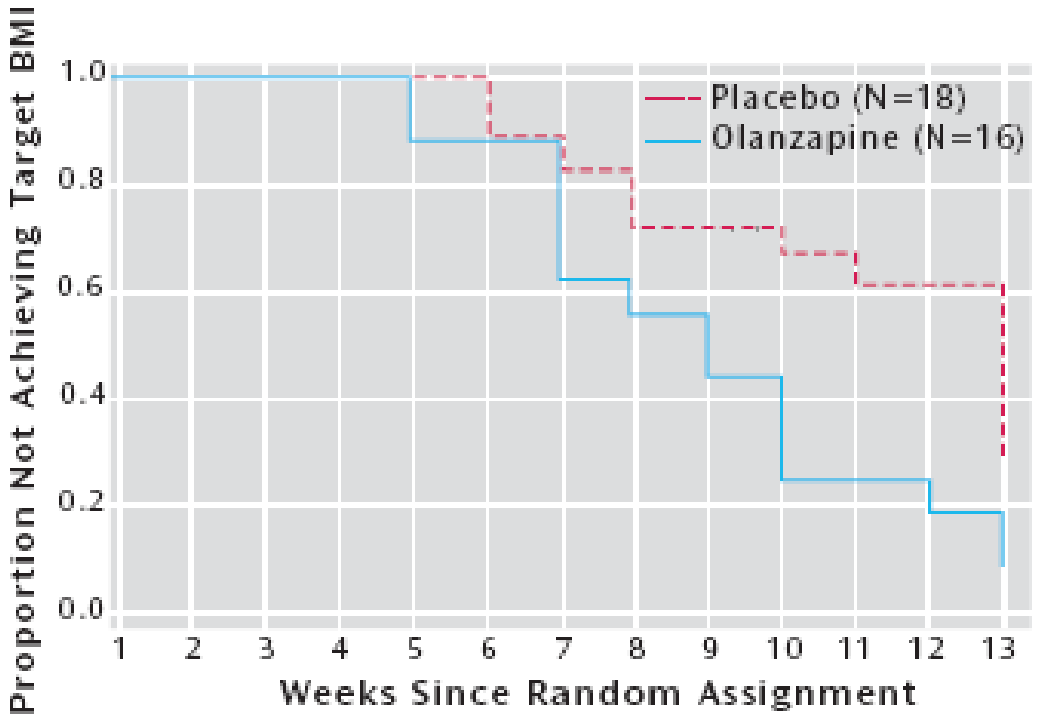
Attia et al, 1998

Anorexia Nervosa
Controlled Trial of Olanzapine

- The next slide shows data from a recent trial of olanzapine used in conjunction with a day program to accelerate weight gain.
  - The data are presented as the fraction of patients who have *failed* to achieve a minimally normal weight over time; this fraction falls faster on olanzapine.
- This is a small trial, but suggests that olanzapine may be of benefit. Patient compliance may be an issue.

Olanzapine vs. Placebo in Anorexia Nervosa

FIGURE 2. Comparison of Treatment Conditions in Time to Achievement of Target Body Mass Index (18.5 kg/m^2)[a]



[a] Kaplan-Meier survival curves analysis indicated a significant difference between groups (Mantel-Cox test: χ^2=5.31, df=1, p=0.02).

Bisada et al, Am J Psychiatry, 2008.

Anorexia Nervosa: Summary of Controlled Medication Trials in Underweight Patients

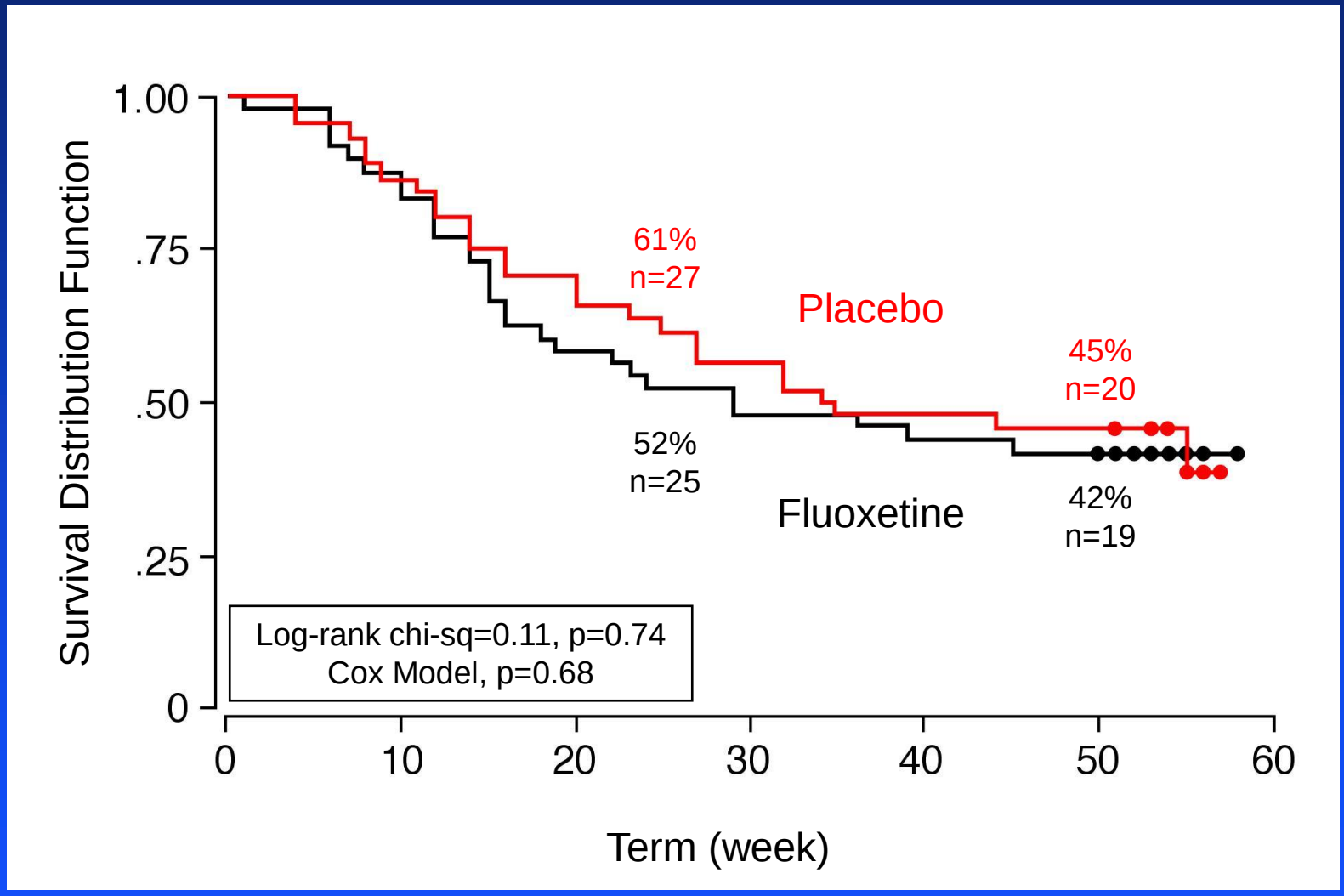
- Very small number of trials.
- But, *no* convincing evidence of utility of any medication.

  Olanzapine intriguing—more data needed.
- Might malnutrition cause neurochemical changes that interfere with actions of medications?
- Therefore, examine the utility of medications to prevent relapse.

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**
- **Walsh, Kaplan, et al (2006)**
  - **93 weight-restored patients, all receiving CBT**
  - **Fluoxetine vs Placebo**
  - **No evidence of benefit (see next slide)**

Fluoxetine vs Placebo
Dropout = Relapse



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**

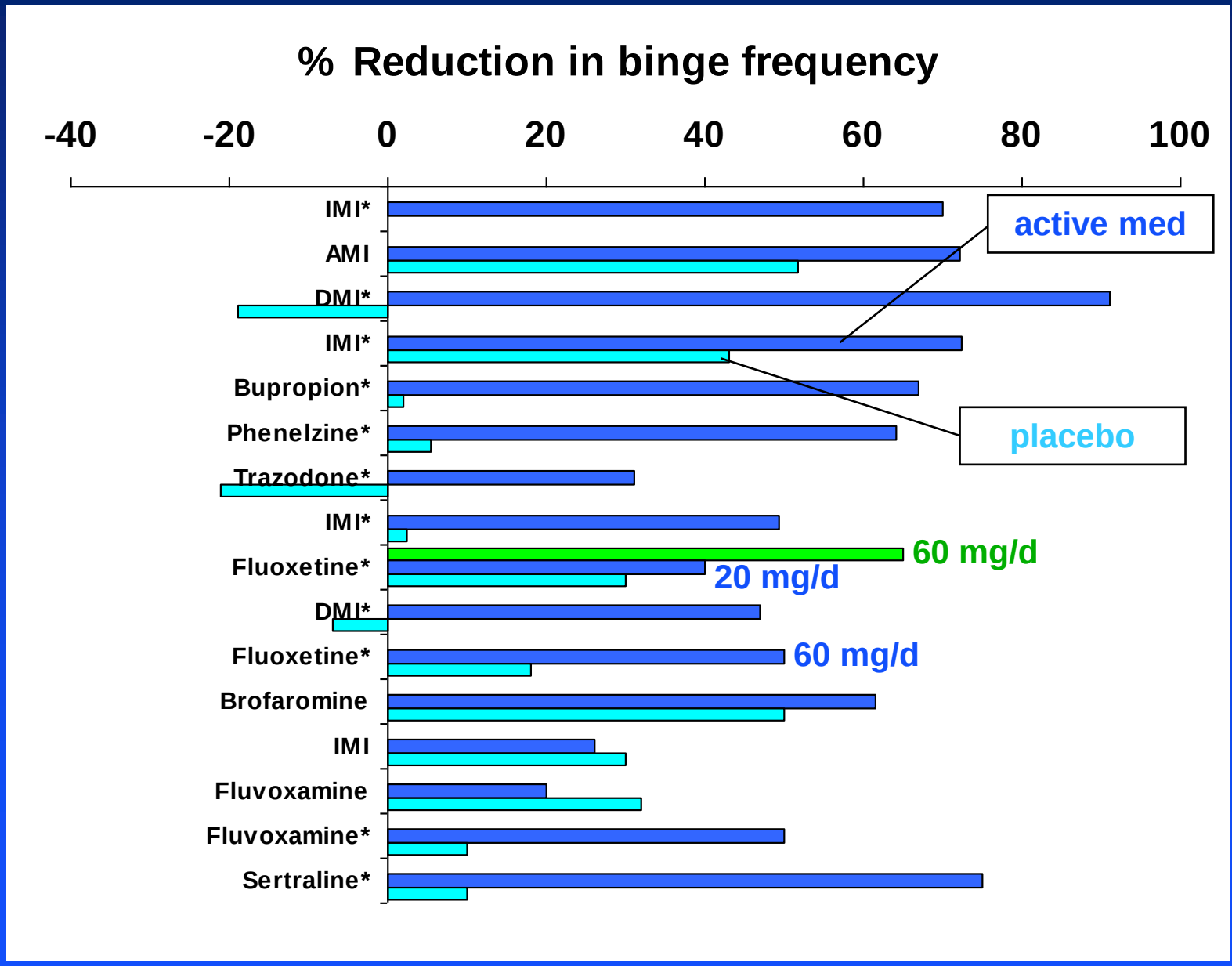
Bulimia Nervosa
Rationale for Antidepressants

- Comorbidity with depression
- Role of serotonin in satiety

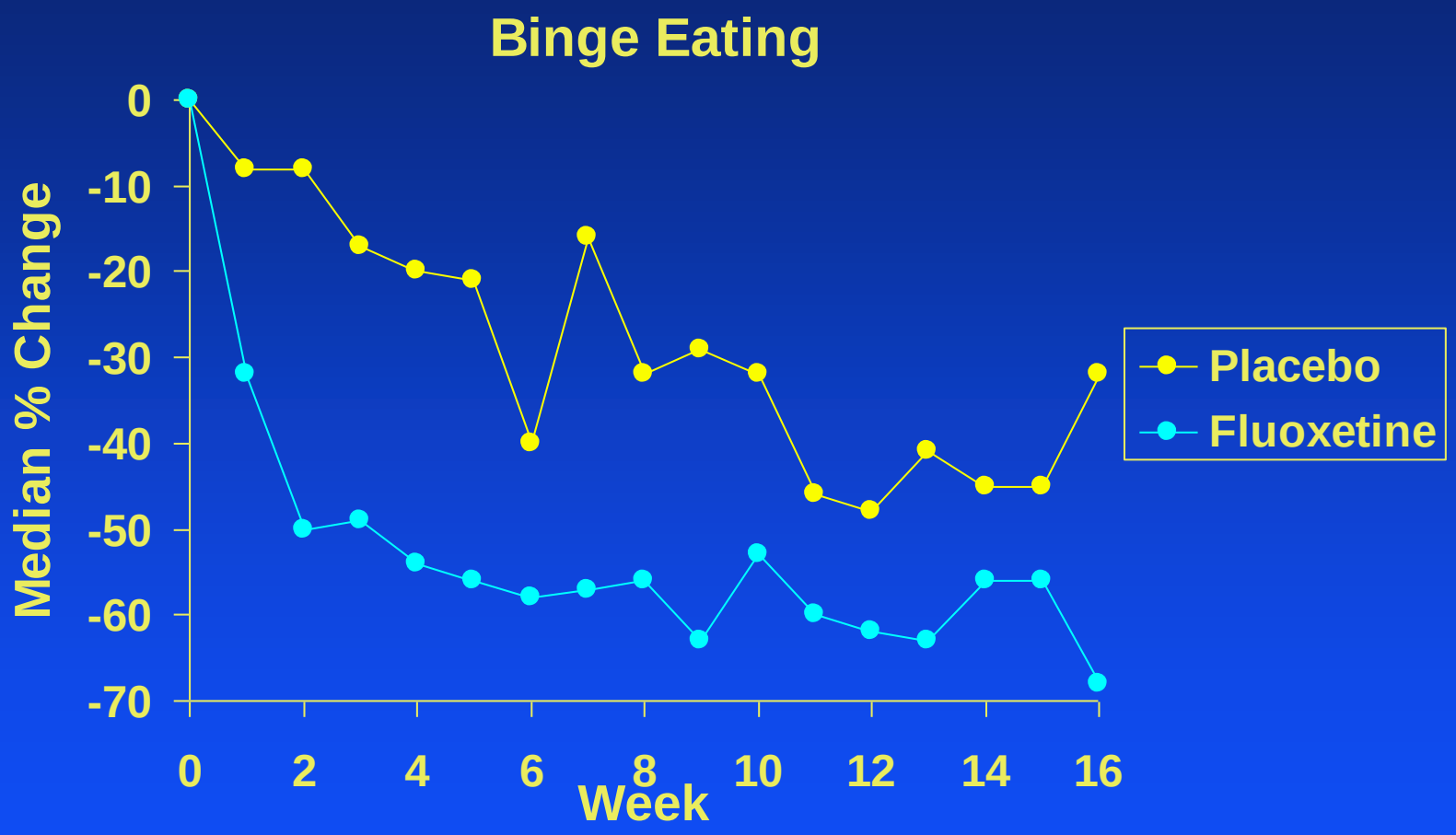
Controlled Trials of Antidepressants in Bulimia Nervosa

Author	Medication	n	Length(wks)
Sabine et al	Mianserin	36	8
Pope et al	Imipramine	19	8
Mitchell & Groat	Amitriptyline	32	8
Hughes et al	Desipramine	22	6
Walsh et al	Phenelzine	50	6
Agras et al	Imipramine	22	16
Kennedy et al	Isocarboxazid	18	6
Barlow et al	Desipramine	24	6
Blouin et al	Desipramine	10	6
Horne et al	Bupropion	49	8
Pope et al	Trazodone	42	6
Mitchell et al	Imipramine	74	10
Enas et al	Fluoxetine	382	8
Walsh et al	Desipramine	78	6
Wheadon et al	Fluoxetine	390	16
Kennedy et al	Brofaromine	36	8
Alger et al	Imipramine	22	8
Schmidt et al	Fluvoxamine	267	8
Milano et al	Fluvoxamine	12	12
Milano et al	Sertraline	20	12

Antidepressant Treatment of Bulimia Nervosa



Bulimia Nervosa: Time Course of Response to Fluoxetine



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 at 60 mg/d is clearly 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
(single study—not replicated)

Topiramate

Topiramate for Bulimia Nervosa

- **Topiramate**

  Effective anti-epileptic.

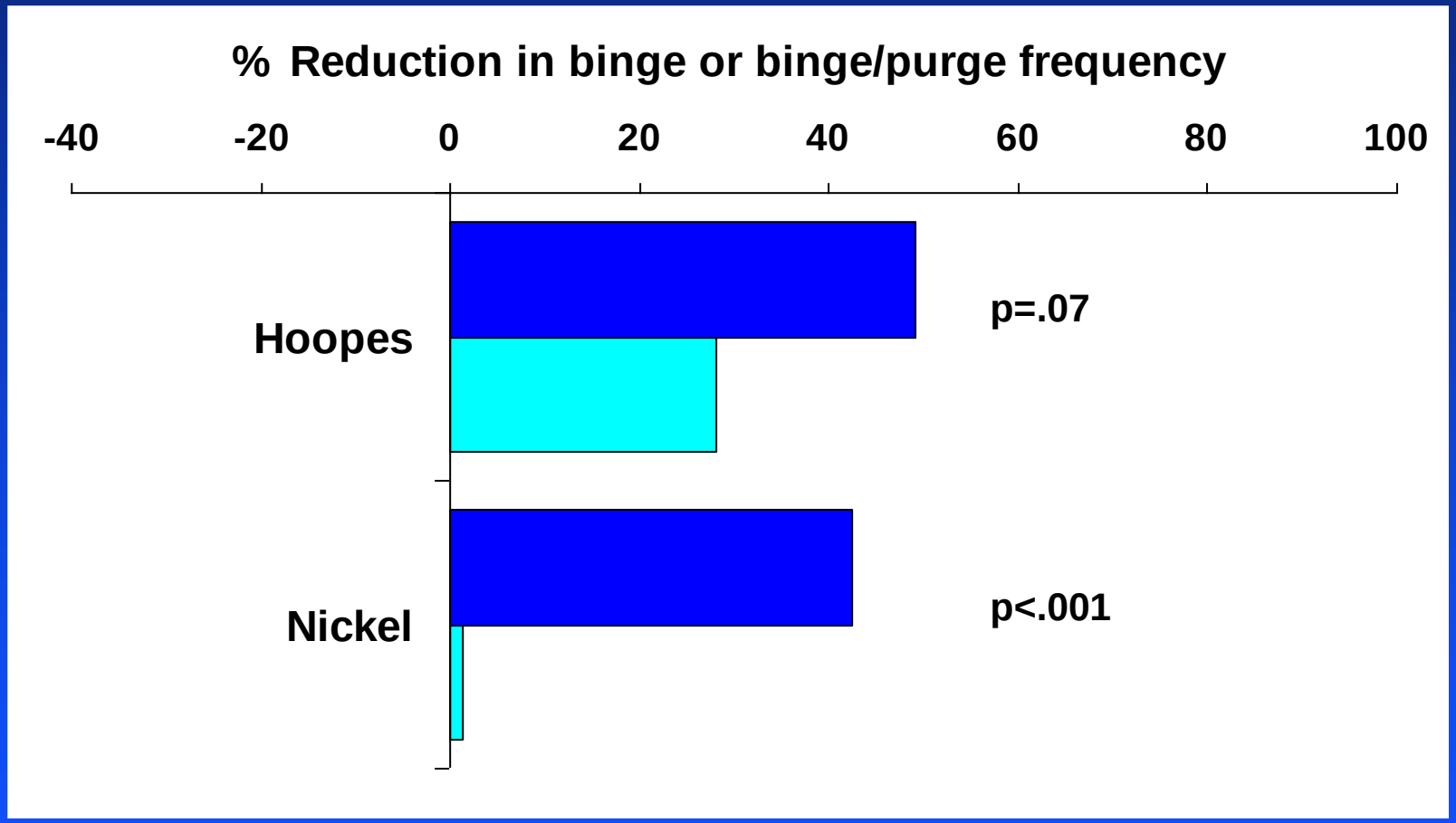
  Appears effective in obesity.

  Two placebo controlled trials support efficacy (see next slide).

  Side effects (e.g., cognitive slowing, paresthesias, kidney stones) potentially problematic.

Topiramate Treatment of Bulimia Nervosa

(Hoopes et al, 2003; Nickel et al, 2005)



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**

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*. 4th ed. Text revision. 2000:785-787.

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)

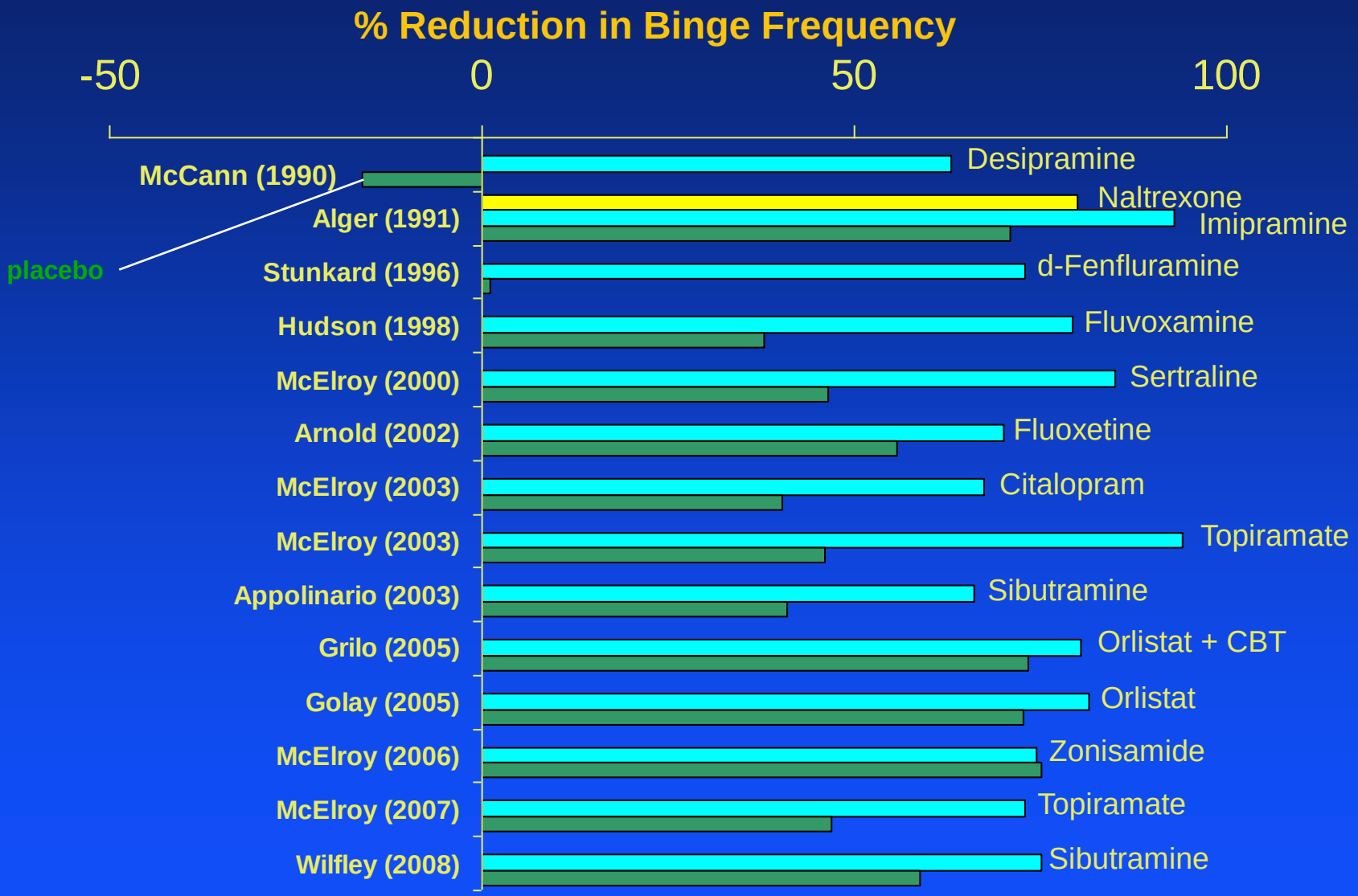
Medications Examined for Treatment of BED

- Antidepressants
  - TCAs: desipramine, imipramine
  - SRIs: fluvoxamine, sertraline, fluoxetine, citalopram
- FDA approved antiobesity agents
  - sibutramine
  - orlistat
- Other
  - Naltrexone
  - Topiramate
  - Zonisamide

Controlled Medication Trials in BED

Author	Medication(s)	N	Length (weeks)
McCann (1990)	Desipramine	23	12
Alger (1991)	Imipramine Naltrexone	55	8
Stunkard (1996)	d-Fenfluramine*	28	8
Hudson (1998)	Fluvoxamine	85	9
McElroy (2000)	Sertraline	34	6
Arnold (2002)	Fluoxetine	60	6
McElroy (2003)	Citalopram	38	6
McElroy (2003)	Topiramate	58	14
Appolinario(2003)	Sibutramine	60	12
Grilo (2005)	Orlistat + CBT	50	12
Golay (2005)	Orlistat	89	24
McElroy (2006)	Zonisamide	60	16
McElroy (2007)	Topiramate	394	16
Wilfley (2008)	Sibutramine	304	24

Efficacy of Medication for Treatment of BED



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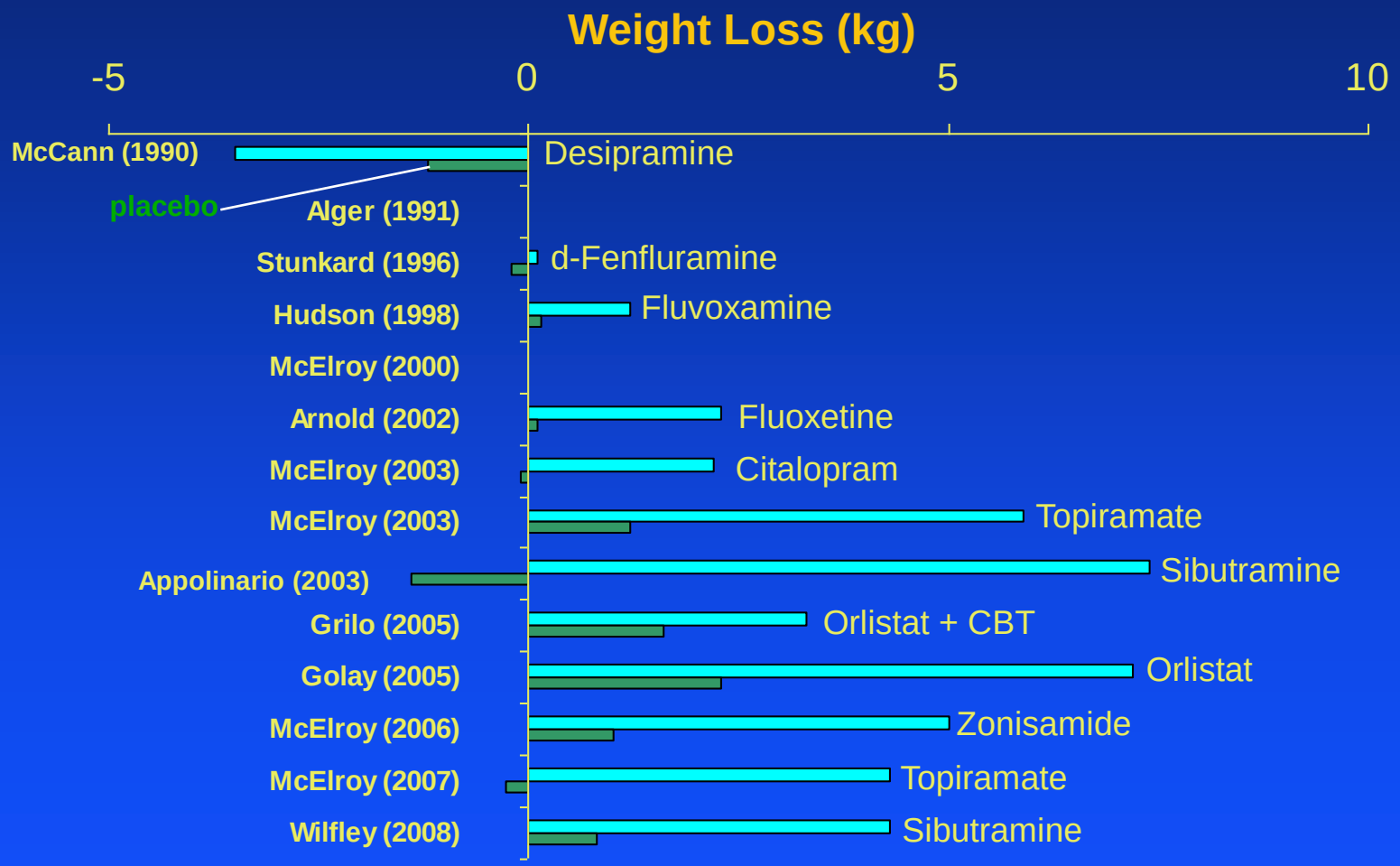
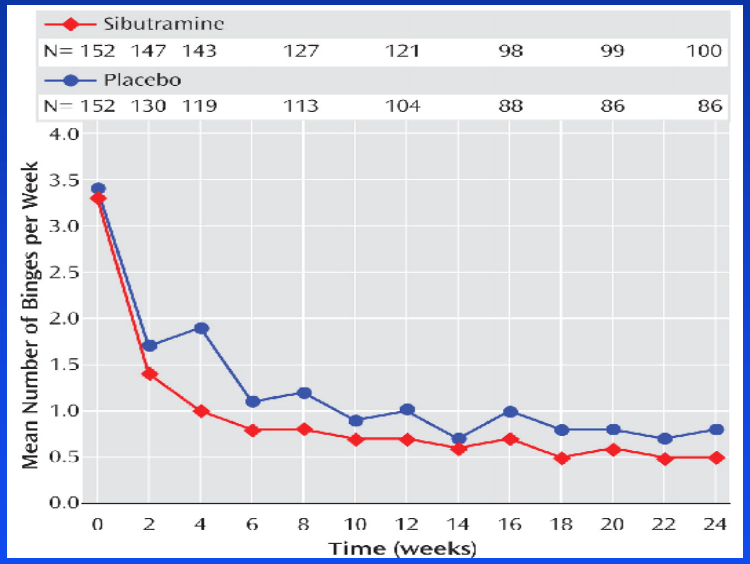


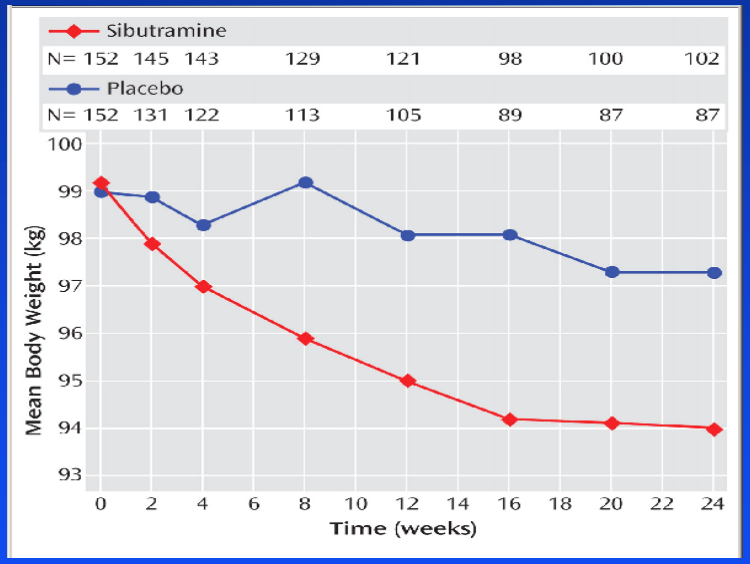
Example: Sibutramine for BED

(Wilfley et al, 2008)

Binge Eating



Weight



Conclusions: Treatment of Binge Eating Disorder

- A range of treatments appears effective in reducing binge eating frequency and improving symptoms of mood disturbance.
  - Several forms of psychological treatment are also 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 at 60 mg/d).**
  - **Second line: SNRI? Topiramate?**
- **Binge Eating Disorder**
  - **Many interventions appear helpful, but best approach is uncertain at present.**

Unsolicited Advertisements

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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4. In controlled trials, at least one-half of the anti-bulimic effect of fluoxetine is apparent within (choose the shortest correct answer):

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

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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