Benefit/Risk Evaluation

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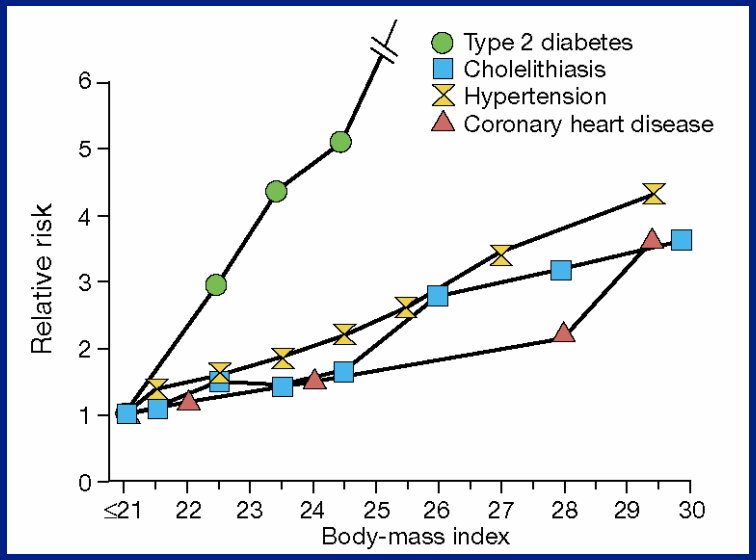
Rimonabant: Benefit and Risk

- Therapeutic need
- Benefits of treatment
- Risks of treatment
  - screening
  - identifying
  - managing
- Benefit/risk assessment

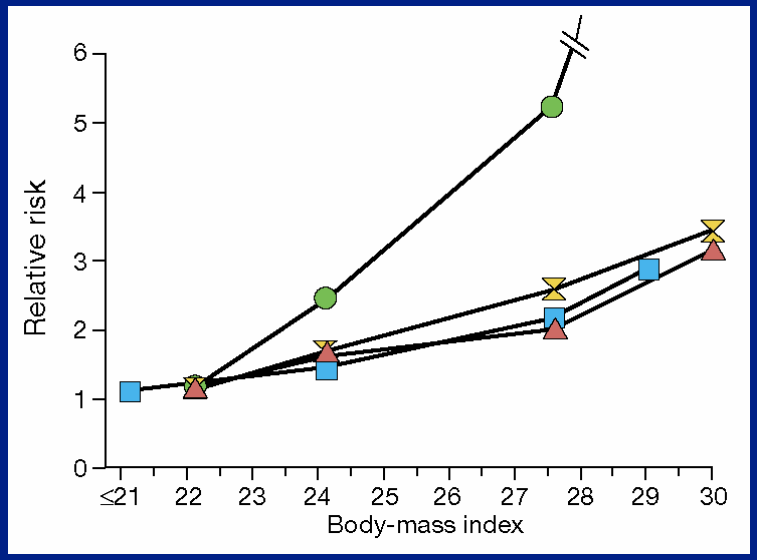
Rimonabant Addresses a Medical Need

- Obesity is a leading cause of both diabetes and heart disease
- Current treatments for diabetes and heart disease don't address the underlying obesity

Women



Men



- AHA/ADA Statement on Prevention of CV Disease in DM
  - Risk factor assessment should include obesity
  - Risk factor reduction should include weight loss in obese and overweight patients

Willett WC, et al. *N Engl J Med.* 1999;341:427-434.

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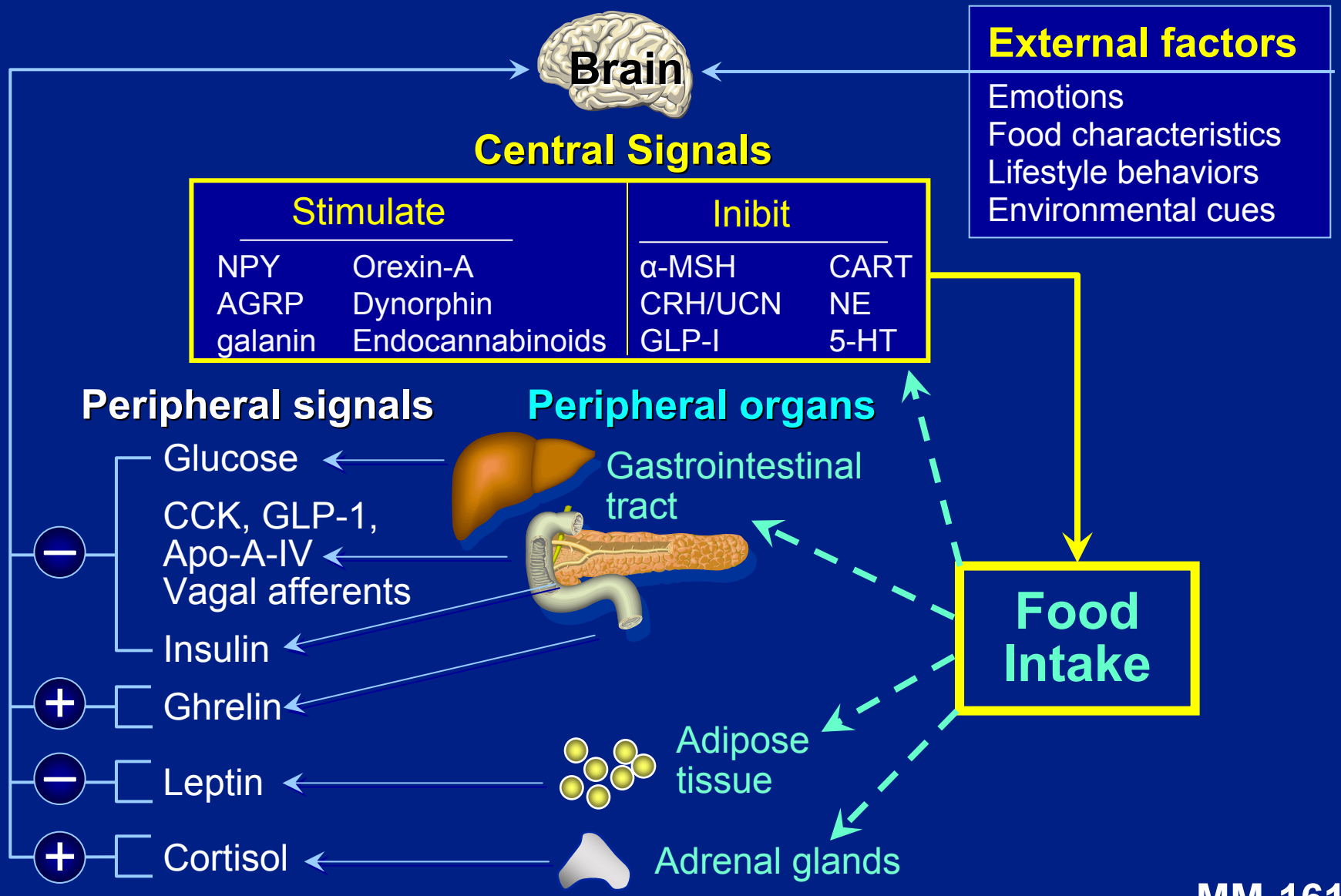
Treatment Options

Therapy	Example of Risk
No Treatment	Development of type 2 diabetes, CVD
Non-prescription, Herbal, Dietary Supplements	Limited evidence of safety and efficacy
Diet, Exercise, Behavior	Treatment of choice, but high rate of relapse
Pharmacotherapy	Orlistat and Sibutramine
Gastric Banding Surgery	BMI ≤ 35 Nausea, reflux, 8% re-operation, 0.4% mortality

McBride BF, et al. *JAMA.* 2004;291(2):216-221. Nisoli E, Carruba MO. *Obes Rev.* 2000;1(2):127-139. Klein S. Gastroenterology 2002;123:882–932. Angrisani L et al, *Obesity Surgery,* 2004,**14**, 415-418. The Lap-Band® Adjustable Gastric Banding System Summary of Safety and Effectiveness Data. http://www.fda.gov/Ohrms/Dockets/Ac/05/Briefing/2005. http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3625t1.rtf (Full transcript) Accessed June 7, 2007.

Weight is Controlled by a Complex Feedback System: Weight Loss Itself Provokes Counterregulatory Responses



Adapted from Schwartz MW, et al. Nature 2000;404:661-671. Source: www.obesityonline.org

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Benefits of Rimonabant

- Sustained weight loss up to 2 years
- Body weight and traditional risk factors
  - Triglycerides
  - HDL cholesterol
  - Markers of inflammation
  - IWQoL
  - In diabetes
    - Glucose
    - HbA1C

Rimonabant Risk Assessment

- Safety profile characterized in clinical trials
  - 3 body systems:
    - psychiatric
    - central nervous system
    - gastrointestinal
- Psychiatric adverse events of interest
  - depression
  - anxiety

Incidence of Side Effects Within Class

Sibutramine Prescribing Information

	Sibutramine	Placebo
Nausea	5.9%	2.8%
Depression	4.3%	2.5%
Anxiety	4.5%	3.4%

Orlistat Prescribing Information

	Orlistat 120		Placebo
Nausea	Yr 1 Yr 2	8.1% 3.6%	7.3% 2.7%
Depression	Yr 1 Yr 2	---- 3.4%	---- 2.5%
Anxiety	Yr 1 Yr 2	4.7% 2.8%	2.9% 2.1%

Rimonabant (Obesity Program)

	Rimonabant	Placebo
Nausea	13.6%	4.7%
Depression	3.9%	1.7%
Anxiety	5.9%	2.1%

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Validated 2-question Initial Screening Test for Depression

During the past month:

1. Have you often been bothered by feeling down, depressed, or hopeless? *Yes* *No*
2. Have you often been bothered by little interest or pleasure in doing things? *Yes* *No*

***Interpretation:** Positive screen for depression is answering "Yes" to either question and triggers additional assessment*

Sensitivity: 83% for Major Depression
Specificity: 92% for Major Depression

Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: Validity of a two-item depression screener. Med Care 2003;41:1284-92.

Rimonabant
Benefit-Risk Conclusion

- An addition to the armamentarium of tools for managing obese patients with health problems
  - Addresses pathophysiology of obesity and its metabolic consequences
  - Reduces body weight and improves multiple risk factors; improves quality of life
  - Should reduce risk of Type 2 DM
- Safety profile defined, further evaluation continues in outcome trials and pharmacovigilance
- Plan for minimizing risk
  - Education of patients, healthcare providers
  - Screening for depression, suicidality
  - Strategy for monitoring, management