The Obesity Challenge: Update in Weight Loss Medications
3rd Annual APN Pharmacology Update 2015

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Disclosure of Financial Relationships

Put Name Here

Has no relationships with any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.
Prevalence and Trends
Definitions
Exercise
Nutrition
Treatment – Medical
Treatment – Surgical
Future Developments
### Obesity by the Numbers

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight U.S. adults</td>
<td>67%</td>
</tr>
<tr>
<td>U.S. adults with obesity</td>
<td>33%</td>
</tr>
<tr>
<td>U.S. children with obesity</td>
<td>17%</td>
</tr>
<tr>
<td>Annual U.S. health care expenditures for obesity</td>
<td>&gt; $ 200 billion</td>
</tr>
<tr>
<td>U.S. consumer expenditures for weight loss products</td>
<td>&gt; $ 50 billion</td>
</tr>
<tr>
<td>Daily deaths from obesity complications</td>
<td>&gt; 1,000</td>
</tr>
</tbody>
</table>
Disproportionate Increase in Severe Obesity

Today, more than 1.7 million US adults with BMI > 50
We Ain’t Seen Nothin’ Yet!
Childhood Obesity in the USA

Prevalence of High BMI for Age in Boys and Girls Aged 6 Through 19 Years.
“There has been a slowing down in the rate of increase but the prevalence remains very high.”

Obesity Trends* Among U.S. Adults
BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1986

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1987

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1988

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1989

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1990

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1991

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1992

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1993

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1994

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1995

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1996

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1997
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1998

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1999

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2000

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2001

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2002
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2003

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2004

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2006

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2007

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2008

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2009

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2010

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Prevalence* of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2011

*Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.
Prevalence* of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2012

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Prevalence* of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2013

*Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.
### Prevalence* of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2013

<table>
<thead>
<tr>
<th>State</th>
<th>Prevalence</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alabama</td>
<td>32.4</td>
<td>(30.8, 34.1)</td>
</tr>
<tr>
<td>Alaska</td>
<td>28.4</td>
<td>(26.5, 30.4)</td>
</tr>
<tr>
<td>Arizona</td>
<td>26.8</td>
<td>(24.3, 29.4)</td>
</tr>
<tr>
<td>Arkansas</td>
<td>34.6</td>
<td>(32.7, 36.6)</td>
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<tr>
<td>California</td>
<td>24.1</td>
<td>(23.0, 25.3)</td>
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<tr>
<td>Colorado</td>
<td>21.3</td>
<td>(20.4, 22.2)</td>
</tr>
<tr>
<td>Connecticut</td>
<td>25.0</td>
<td>(23.5, 26.4)</td>
</tr>
<tr>
<td>Delaware</td>
<td>31.1</td>
<td>(29.3, 32.8)</td>
</tr>
<tr>
<td>District of Columbia</td>
<td>22.9</td>
<td>(21.0, 24.8)</td>
</tr>
<tr>
<td>Florida</td>
<td>26.4</td>
<td>(25.3, 27.4)</td>
</tr>
<tr>
<td>Georgia</td>
<td>30.3</td>
<td>(28.9, 31.8)</td>
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<tr>
<td>Guam</td>
<td>27.0</td>
<td>(24.4, 29.8)</td>
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<tr>
<td>Hawaii</td>
<td>21.8</td>
<td>(20.4, 23.2)</td>
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<td>Idaho</td>
<td>29.6</td>
<td>(27.8, 31.4)</td>
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<tr>
<td>Illinois</td>
<td>29.4</td>
<td>(27.7, 31.2)</td>
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<tr>
<td>Indiana</td>
<td>31.8</td>
<td>(30.6, 33.1)</td>
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<tr>
<td>Iowa</td>
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<td>(29.9, 32.7)</td>
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<td>(29.2, 30.7)</td>
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<td>Kentucky</td>
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<td>(31.8, 34.6)</td>
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<td>(31.1, 35.2)</td>
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<td>28.9</td>
<td>(27.5, 30.2)</td>
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<td>Massachusetts</td>
<td>23.6</td>
<td>(22.5, 24.8)</td>
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<tr>
<td>Michigan</td>
<td>31.5</td>
<td>(30.4, 32.6)</td>
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<td>Minnesota</td>
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<td>(24.1, 26.8)</td>
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<tr>
<td>Mississippi</td>
<td>35.1</td>
<td>(33.5, 36.8)</td>
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</table>

<table>
<thead>
<tr>
<th>State</th>
<th>Prevalence</th>
<th>Confidence Interval</th>
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<tbody>
<tr>
<td>Missouri</td>
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<td>(28.8, 32.1)</td>
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<td>Montana</td>
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<td>(23.4, 25.8)</td>
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<tr>
<td>Nebraska</td>
<td>29.6</td>
<td>(28.4, 30.7)</td>
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<tr>
<td>Nevada</td>
<td>26.2</td>
<td>(24.0, 28.6)</td>
</tr>
<tr>
<td>New Hampshire</td>
<td>26.7</td>
<td>(25.3, 28.3)</td>
</tr>
<tr>
<td>New Jersey</td>
<td>26.3</td>
<td>(25.1, 27.5)</td>
</tr>
<tr>
<td>New Mexico</td>
<td>26.4</td>
<td>(25.1, 27.7)</td>
</tr>
<tr>
<td>New York</td>
<td>25.4</td>
<td>(24.2, 26.6)</td>
</tr>
<tr>
<td>North Carolina</td>
<td>29.4</td>
<td>(28.1, 30.7)</td>
</tr>
<tr>
<td>North Dakota</td>
<td>31.0</td>
<td>(29.5, 32.5)</td>
</tr>
<tr>
<td>Ohio</td>
<td>30.4</td>
<td>(29.2, 31.6)</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>32.5</td>
<td>(31.2, 33.9)</td>
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<tr>
<td>Oregon</td>
<td>26.5</td>
<td>(24.9, 28.1)</td>
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<tr>
<td>Pennsylvania</td>
<td>30.0</td>
<td>(28.9, 31.2)</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>27.9</td>
<td>(26.4, 29.5)</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>27.3</td>
<td>(25.8, 28.8)</td>
</tr>
<tr>
<td>South Carolina</td>
<td>31.7</td>
<td>(30.5, 33.1)</td>
</tr>
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<td>South Dakota</td>
<td>29.9</td>
<td>(28.0, 31.8)</td>
</tr>
<tr>
<td>Tennessee</td>
<td>33.7</td>
<td>(31.9, 35.5)</td>
</tr>
<tr>
<td>Texas</td>
<td>30.9</td>
<td>(29.5, 32.3)</td>
</tr>
<tr>
<td>Utah</td>
<td>24.1</td>
<td>(23.2, 25.1)</td>
</tr>
<tr>
<td>Vermont</td>
<td>24.7</td>
<td>(23.4, 26.1)</td>
</tr>
<tr>
<td>Virginia</td>
<td>27.2</td>
<td>(25.9, 28.5)</td>
</tr>
<tr>
<td>Washington</td>
<td>27.2</td>
<td>(26.0, 28.3)</td>
</tr>
<tr>
<td>West Virginia</td>
<td>35.1</td>
<td>(33.6, 36.6)</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>29.8</td>
<td>(28.0, 31.6)</td>
</tr>
<tr>
<td>Wyoming</td>
<td>27.8</td>
<td>(26.2, 29.5)</td>
</tr>
</tbody>
</table>

Source: Behavioral Risk Factor Surveillance System, CDC.

*Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.
The Mirror Does Not Lie

Weight Classification by Body Mass Index (BMI)
Obesity Rate with BMI > 30

Sources:
1. Christiana Care data from Biometric Screening.
2. Delaware and Nationwide data from Office of Surveillance, Epidemiology, and Laboratory Services Behavioral Risk Factor Surveillance System 2013

STOP!
# BMI - A VITAL SIGN

<table>
<thead>
<tr>
<th>BMI</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5 - 25</td>
<td>Normal</td>
</tr>
<tr>
<td>25 - 27</td>
<td>Overweight</td>
</tr>
<tr>
<td>27 - 30</td>
<td>Overweight with risk</td>
</tr>
<tr>
<td>30 - 40</td>
<td>Obese (30 - 34.9 = class I, 35 - 39.9 = class II)</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Morbidly obese (class III)</td>
</tr>
<tr>
<td>or &gt; 35</td>
<td>Morbidly obese (class III)</td>
</tr>
<tr>
<td>&gt; 35 with</td>
<td>two comorbidities</td>
</tr>
</tbody>
</table>
Body Mass Index (BMI)

BMI = \frac{\text{Weight in pounds}}{\text{Height in inches} \times \text{Height in inches}} \times 703
"Your skin is enlarged."
Correlation of BMI With Total Body Fat

Body Mass Index vs. Adipose Tissue (kg)

$r = 0.96; p < 0.001$

Relationship Between BMI and Mortality

Mortality Risk as BMI Increases

- Low risk
- Moderate risk
- High risk

Mortality and Obesity

Years of Life Lost from Overweight and Obesity – Framingham Heart Study: A Life-Table Analysis

Women

<table>
<thead>
<tr>
<th></th>
<th>Non-smokers</th>
<th>Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>3.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Obese</td>
<td>3.1</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Men

<table>
<thead>
<tr>
<th></th>
<th>Non-smokers</th>
<th>Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>3.1</td>
<td>5.8</td>
</tr>
<tr>
<td>Obese</td>
<td>1.3</td>
<td>13.7</td>
</tr>
</tbody>
</table>

Comparison to normal weight nonsmokers

† Comparison to normal weight smokers
The Primary Care Obesity Diagnosis Project:

- 9827 patients underwent a general medical examination by a physician
- 2543 (25.9%) had a BMI of > 30

Impact of Obesity Diagnosis on Management

81.1% of patients with BMI > 30 did not receive a diagnosis of obesity!

If obesity was diagnosed, only 39% of staff MDs and 37% of resident MDs documented an obesity management plan.

Why Is Obesity Increasing So Quickly?

- Genes: probably not

- Environment:
  - Caloric intake
  - Exercise
Heredity and Environment in Obesity Etiology

- Genetics: 40%
- Environment: 60%
Weight and Energy Balance

By the laws of physics...
America's Weapons of Mass Destruction
SEX!!
Now that we have your attention, eat at Subway
Increased Portion Sizes

100 extra cal/day = 10 lbs extra fat by end of year

<table>
<thead>
<tr>
<th></th>
<th>1955</th>
<th>2001</th>
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<tbody>
<tr>
<td>French fries</td>
<td>Only size available 2.3 oz.</td>
<td>Super size 6.9 oz.</td>
</tr>
<tr>
<td>Cola</td>
<td>Only size available 6.5 oz.</td>
<td>Single serve 20 oz.</td>
</tr>
<tr>
<td>Chocolate bar</td>
<td>Only size available 1.1 oz.</td>
<td>The Big One 3.7 oz.</td>
</tr>
</tbody>
</table>

Want to take a walk?
## Examples of Energy Expenditures

<table>
<thead>
<tr>
<th>Sedentary</th>
<th>Kcal</th>
<th>Active</th>
<th>Kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using TV remote</td>
<td>&lt;1</td>
<td>Changing the channel</td>
<td>3</td>
</tr>
<tr>
<td>Garage door opener</td>
<td>&lt;1</td>
<td>Raising garage door</td>
<td>3</td>
</tr>
<tr>
<td>Waiting 30 min for pizza</td>
<td>15</td>
<td>Cooking for 30 min</td>
<td>25</td>
</tr>
<tr>
<td>Elevator up 3 flights</td>
<td>0.3</td>
<td>Walking 3 flights</td>
<td>15</td>
</tr>
<tr>
<td>Paying at the pump</td>
<td>0.6</td>
<td>Walking in to pay</td>
<td>5</td>
</tr>
<tr>
<td>Buying presliced veg.</td>
<td>0</td>
<td>Chopping veg., 30 min</td>
<td>12</td>
</tr>
<tr>
<td>30 min. of telephone, sitting</td>
<td>4</td>
<td>30 min. of telephone, standing</td>
<td>20</td>
</tr>
<tr>
<td>Sitting through 30min. lecture</td>
<td>60</td>
<td>Giving lecture</td>
<td>70</td>
</tr>
</tbody>
</table>

*Blair, Mayo Clin Proc. 2002;77:109*
Health Risks Associated With Obesity

- Diabetes mellitus
- Hypertension
- Dyslipidemia
- Coronary heart disease
- Thromboembolic disease - stroke
- Restrictive lung disease
- Degenerative arthritis
- Gallbladder disease
- Cancer: endometrial, breast, prostrate, colon

- Premature death
- Congestive heart Failure
- GERD
- Gout
- NASH
- Pregnancy complications
- Menstrual irregularities
- Bladder control problems, stress incontinence
- Infertility
- Psychological disorders – depression, eating disorder, low self-esteem, distorted body image
Modest weight reduction, in the range of 5% to 10% of initial body weight, is sufficient to IMPROVE:

- Hypertension\(^1\)
- Lipid abnormalities\(^2\)
- Glycemic control\(^3\)

Why Try?

A sustained 10% reduction in body weight:

- Reduces expected CHD by > 4% and reduces CVA
- Increases life expectancy by 7 months
- Reduces lifetime medical costs by up $5300
- Reduces risk of dying in the next year by 25%

A sustained weight loss greater than 10% is usually not realistic, and should not be routinely prescribed.

- With a weight loss > 10%, metabolism may slow, and hunger may rise.

Oster et al Am J Public Health 1999;89:1536
• Ghrelin is released during fasting and initiates eating behavior.

• Other peptides are released postprandially in response to vagal efferents triggered by stretch receptors.

• These include PYY, GLP-1, oxyntomodulin, pancreatic polypeptide, GLP-1, CCK and amylin.

• Leptin seems to be an anti-starvation hormone involved in long term energy regulation.
Executive summary: Guidelines (2013) for the management of overweight and obesity in adults

[Diagram of the management process]

Obesity
Volume 22, Issue S2, pages S5-S39, 24 JUN 2014 DOI: 10.1002/oby.20821
Treatment Algorithm for Achieving and Maintaining ≥5% Weight Loss

1. Determine weight loss ≥5% and sufficient improvement in health targets
   - YES
   - NO

   2. Follow-up and weight loss maintenance
      - YES
      - NO

   3. Intensive behavioral treatment
      - Reassess and address medical and other factors
      - Consider pharmacotherapy
      - Refer for bariatric surgery

4. Weight loss ≥5% and sufficient improvement in health targets
   - YES
   - NO

   5. Continue intensive medical management of CVD risk factors and obesity-related conditions
      - Refer for bariatric surgery

   Measure BMI at least annually

BMI = body mass index

Advise Devise Strategy With Patient

- **No Clinical Inertia!**

- Communicate that weight loss of 10% achieves significant health benefits
  - Ex: In the Diabetes Prevention Program an average 7% weight loss reduced the onset of type 2 diabetes by 58%.¹
  - Ex: Possible to reduce other meds with weight loss

- Set realistic goals:
  - 1–2 lb per week over 6 months according to NIH²

---

Assist
Establish Appropriate Intervention

- Therapeutic Lifestyle Change (TLC)
- Pharmacotherapy
- Surgery
Implementation at the PCP Level

- Maintaining an active dietary record.
- **Daily** physical activity, recorded.
- Regular weigh ins with dietitians, MA, LPN.
- Don’t prescribe drugs without additional support.
Medication + Lifestyle Modification

Intention-to-Treat Analysis*

Weight Loss (kg)

Sibutramine alone
Lifestyle modification alone
Sibutramine + brief therapy
Combined therapy

Weeks

0 3 6 10 18 40 52

* A last-observation-carried-forward analysis yielded the same statistical conclusions.

Implementation at the PCP Level

- Define success, and set a realistic goal. Encourage acceptance of biologically realistic outcomes.
- Patient’s usually want a greater weight loss than is biologically realistic. Emphasize the health benefits of a modest amount of weight loss.
- Adherence: be concrete. “eat less, exercise more” does not work.
Implementation at the PCP Level

- The period of active weight loss (usually up to 6 months or so) is followed by a lifelong period of weight maintenance.
- Different skills and approaches are needed for each phase.
Different goals: “lose a lot” during weight loss vs. “don’t gain it back” during maintenance.

Exercise is helpful during weight loss.

Exercise is mandatory during weight maintenance.
Implementation at the PCP level

Watch for common mistakes:

- Setting unrealistic goals.
- Ignoring personal preferences.
- Ignoring lessons from past experiences.
- Starting too vigorously.
- Self criticism.
Implementation at the PCP Level

- Don’t forget the exercise prescription.
- Physical activity independent of obesity lowers the risk of heart disease, type 2 diabetes and death.
Assist
Establish Appropriate Intervention

- Therapeutic Lifestyle Change (TLC)
  - Exercise
Drive-by dog walk

Levester Johnson takes his dog, Armani, an Italian Cane Corso, out for a morning jog on Monday, March 26, in Akron, Ohio. "I was lazy this morning," said Johnson. "I'm on the way to the gym myself. I wanted to make sure [Armani] got in a workout before I left."
"My doctor wants me to walk a mile after every meal. But, frankly, ten miles a day is killing me."
Some Statistics

- Fitness and Cardiac exercise programs typically report dropout rates ranging from 9 to 87%.
- Dropout rates are generally highest in the first 3 months, increasing to approximately 50% within one year.
STRRIDE: Vigorous physical activity may be required for significant weight loss

STRRIDE = Studies of Targeted Risk Reduction Interventions through Defined Exercise (N = 120)

Δ Weight (%)

-4  -2  0  2

Control  Low amount/ Moderate intensity  Low amount/ Vigorous intensity  High amount/ Vigorous intensity

*P < 0.05 vs control, †P < 0.05 vs high-amount group

Exercise amount (miles/week): Control ≈ 0, Low ≈ 12, High ≈ 20
Exercise intensity (peak O₂ consumption):
Moderate = walking (40-55%), Vigorous = jogging (65-80%)

Dietary Education

- Prescribe a diet:
  - Education
  - Maintainance
To lose weight.....
Keep your ASS out of the Refrigerator!

THE DONKEY DIET
Weight Loss at 2 Years: Males

- All Subjects: 
  - Low Fat: $-2.9 \pm 4.2$ kg
  - Mediterranean: $-4.4 \pm 6.0$ kg
  - Low Carb: $-4.7 \pm 6.5$ kg

- Women:
  - Low Fat: $-0.1$ kg
  - Mediterranean: $-6.2$ kg
  - Low Carb: $-2.4$ kg
<table>
<thead>
<tr>
<th>Diet (12 month data)</th>
<th>% Drop Out</th>
<th>% Weight Loss</th>
<th>% Reduction Framingham Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins</td>
<td>48</td>
<td>3.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Ornish</td>
<td>50</td>
<td>6.2</td>
<td>6.6</td>
</tr>
<tr>
<td>Weight Watchers</td>
<td>35</td>
<td>4.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Zone</td>
<td>35</td>
<td>4.6</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Weight loss: p < 0.5 for all diets compared to base line

Framingham scores: p < 0.5 for all except Ornish (P = 0.13)
Comparison of Weight-Loss Diets with Different Compositions of Fat, Protein, and Carbohydrates

- 811 overweight adults were randomized to four different diets and followed for 2 years.
  - Low-fat, average-protein
  - Low-fat, high-protein
  - High-fat, average-protein
  - High-fat, high-protein

Sacks FM, NEJM 2009;360(9):859
• The average weight loss at 2 years was 4 kg.
• Most weight loss occurred in the first 6 months, and was followed by a period of weight gain.
As a result of these studies, we now know which diet is the very best of all...
Conclusions

- The diet that works the best is the one that you stick to.
- None of the diets in these studies were associated with the kind of weight loss that patients want.
Establish Appropriate Intervention

- Therapeutic Lifestyle Change (TLC)
- Pharmacotherapy
- Surgery
### Obesity Pharmacotherapy: A Bad Safety Record

<table>
<thead>
<tr>
<th>Year</th>
<th>Medication</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1893</td>
<td>Thyroid hormone</td>
<td>hyperthyroidism</td>
</tr>
<tr>
<td>1933</td>
<td>Dinitrophenol</td>
<td>cataracts/neuropathy</td>
</tr>
<tr>
<td>1937</td>
<td>Amphetamine</td>
<td>addiction</td>
</tr>
<tr>
<td>1967</td>
<td>Rainbow pills (digitalis &amp; diuretics)</td>
<td>CV sx</td>
</tr>
<tr>
<td>1997</td>
<td>Fenfluramine/Dexfenfluramine</td>
<td>valvulopathy</td>
</tr>
<tr>
<td>2000</td>
<td>Phenylpropanolamine</td>
<td>stroke</td>
</tr>
<tr>
<td>2004</td>
<td>Herbal caffeine &amp; ephedra</td>
<td>CV sx</td>
</tr>
<tr>
<td>2010</td>
<td>Sibutramine</td>
<td>MI and stroke</td>
</tr>
</tbody>
</table>
Pharmacological Treatment of Obesity

- Current medications 5-12% weight loss
- Benefits only last as long as patient takes the medication. Chronic treatment likely needed.
- Drugs probably not paid for by insurance so cost is a big issue for patients.
- Are monotherapy medications an appropriate treatment modality for obesity?
Fenfluramine
1-Year Rx & 1-Year Follow-up

0 mo. 2 mo. 4 mo. 6 mo. 8 mo. 10 mo. 12 mo. 14 mo. 16 mo. 18 mo. 20 mo. 22 mo. 24 mo.

Pounds
Medications

• **Short-term obesity management**
  
  • Sympathomimetics (Phentermine, Diethylpropion, Benzphetamine)

• **Long-term obesity management**
  
  • Lipase inhibitors (Orlistat)

• **Recently approved obesity medications**
  
  • Serotonin agonists (Locaserin)
  
  • Combination agents (Phentermine/Topiramate and Bupropion/Naltrexone)
  
  • GLP-1 RA (Liraglutide 3.0 ml)
Medications

- All medications have responders and non-responders. Unfortunately there are no predictive baseline parameters.
- The change in weight at 3 months is a good predictor.
- If the patient has not had a response (3 – 5% loss), odds are against them being successful with additional exposure to the medication, and it should usually be stopped.
Phentermine

Type: sympathomimetic

Mechanism of action: stimulates the hypothalamus to suppress appetite

Year of approval: 1959

FDA approved indication: short-term (< 12 weeks) adjunct to exercise and caloric restriction for BMI ≥ 30 or ≥ 27 in the presence of other risk factors such as hypertension, diabetes or hyperlipidemia

Efficacy: 3.6 kg mean weight loss beyond that achieved by placebo at 2-24 weeks (meta-analysis of six placebo-controlled trials; Int J Obes Relat Metab Disord 2002;26:262-73)
Phentermine

- **Adverse effects:** risk of dependence and abuse, hypertension, dry mouth, insomnia, tremor, GI disturbance, primary pulmonary hypertension (rare, associated with combined use of fenfluramine in “fen-phen”), valvular heart disease (rare), psychosis (rare)

- **Contraindications:** history of CV disease, MAOIs, hyperthyroidism, glaucoma, history of drug abuse, pregnancy, breastfeeding
Phentermine: A Noradrenergic Drug Reduces Body Weight

Munro JF et al. BMJ 1968;1:352-4
Phentermine

- **Dosing**
  - Phentermine salt (Adipex, Fastin) 18.75 or 37.5 mg once daily.
  - Phentermine resin (Ionamin) 15 or 30 mg daily.

- **Cost:** $35 – 60 per month.
Orlistat (Xenical, Alli)

Type: lipase inhibitor

Mechanism of action: inhibits the breakdown of triglycerides into absorbable free fatty acids by lipase enzymes in the stomach and pancreas, resulting in less fat being absorbed

Year of approval: 1999 (Xenical – prescription 120 mg TID), 2007 (Alli – OTC 60 mg)

FDA approved indication: as an adjunct to a reduced-calorie and low-fat diet for weight loss or to lower the risk of regaining weight after prior weight loss
Efficacy: 2.9 kg mean weight loss (Xenical) beyond that achieved by placebo at one year (meta-analysis of 15 trials; *Ann Intern Med* 2005;142:532-46)

Adverse effects: significant diarrhea, fecal incontinence, oily spotting, flatulence, bloating, dyspepsia (all can be reduced with avoidance of fat-rich foods), reduced absorption of fat-soluble vitamins, serious liver injury (rare)

Contraindications: malabsorption, cholestasis, impaired liver function, pancreatic disease, pregnancy (added in 2012)
Obesity Agents: Orlistat

- FDA approved in 1999
- Gastric and pancreatic lipase inhibitor
- Reduces absorption of ~30% of dietary fat
- 2-year efficacy and safety data
  - Weight loss
  - Weight maintenance
- TID dosing with meals
  - Vitamin supplement recommended
Orlistat: Mechanism of Action
Weight loss with orlistat: Meta-analysis

n = 4948 treated, n = 4509 control

Study or subcategory
- Derosa 2003
- Krempf 2003
- Swinburn 2005
- Hollander 1998
- Sjostrom 1998
- Davidson 1999
- Finer 2000
- Hauptman 2000
- Rossner 2000
- Bakris 2002
- Broom 2002
- Kelley 2002
- Miles 2002
- XENDOS
- Overall effect
  - P < 0.001

Weighted mean difference (random) (95% CI)

XENDOS = Xenical in the Prevention of Diabetes in Obese Subjects

## Orlistat: Change in cardiometabolic parameters

<table>
<thead>
<tr>
<th>Change in:</th>
<th>N</th>
<th>Weighted mean difference (treatment – placebo) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC (in)</td>
<td>4631</td>
<td>-0.81 (-1.13 to -0.50)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1276</td>
<td>-1.05 (-1.40 to -0.71)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)*</td>
<td>1678</td>
<td>-18.56 (-26.84 to -10.27)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>6965</td>
<td>-1.52 (-2.19 to -0.86)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>8322</td>
<td>-1.38 (-2.03 to -0.74)</td>
</tr>
<tr>
<td>Total-C (mg/dL)</td>
<td>5206</td>
<td>-12.37 (-14.31 to -10.83)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>5206</td>
<td>-10.05 (-11.60 to -8.51)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>4152</td>
<td>-1.16 (-1.55 to -0.77)</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>4456</td>
<td>-2.66 (-10.63 to 6.20)</td>
</tr>
</tbody>
</table>

*In those with diabetes  
DBP = diastolic BP, SBP = systolic BP,  
Total-C = total cholesterol, WC = waist circumference  

Orlistat: Adverse Events $\geq 5\%^*$

*Defined as an incidence of $\geq 5\%$ and twice the frequency of the placebo group.

- Oily spotting
- Flatus with discharge
- Fecal urgency
- Fatty/Oily stool
- Oily evacuation
- Increased defecation
- Fecal incontinence

Orlistat OTC: “Alli”

- 60 mg tid instead of 120 mg
- 2 year follow up: 3 kg weight loss compared to placebo.

Rucker D et al, BMJ 2007;335:1194
Orlistat

• Dosing
  • Xenical 120 mg tid/ac
  • Alli 60 mg tid/ac

• Cost
  • Xenical $533/month
  • Alli $51/month
Lorcaserin (Belviq)

Type: serotonin agonist

Mechanism of action: activates 5-HT$_{2C}$ receptors in the hypothalamus, resulting in increased proopiomelanocortin (POMC) production, which promotes satiety

Year of approval: 2012

FDA approved indication: treatment of obesity for adults with BMI $\geq$ 30 or $\geq$ 27 in the presence of other risk factors such as hypertension, diabetes or hyperlipidemia
Lorcaserin (Belviq)

Efficacy: 3.6 kg mean weight loss beyond that achieved by placebo (5.8 kg vs. 2.2 kg) at one year (Phase 3 RCT; *N Engl J Med* 2010; 363:245-256)

Adverse effects: headache, nasopharyngitis

Contraindications: pregnancy, MAOIs, SSRIs (caution)
Lorcasarin (Belviq)

- Serotonin 2C receptor agonist
- Previous serotonin agonists fenfluramine and dexfenfluramine caused cardiac valve disease, removed from market
- 2C receptor only in the brain not in heart
- Studies in 1-2,000 people for up to 2 years do not show evidence of valvulopathy with lorcasarin.
Lorcaserin: Weight Effects

Body Weight during Yr 1

Placebo (N=1499)

Lorcaserin (N=1538)

Study Week

Lorcasarin (Belviq)

- Weight loss: 3-5% no better than phentermine or orlistat
- Side effects: headache, dizziness and nausea
- Cost: $220/month
- Unclear if physicians will prescribe off label with phentermine (no data on safety or efficacy)
Lorcasarin (Belviq)

- Dosing: 10 mg bid
- Cost: $210 – 220/month
Phentermine-topiramate (Qsymia)

Year of approval: 2012

FDA approved indication: chronic weight management, as an adjunct to a reduced-calorie diet and exercise, for BMI ≥ 30 or ≥ 27, in the presence of other risk factors such as hypertension, diabetes or hyperlipidemia
Phentermine/Topiramate ER

- **Brand name:** *Qsymia*
- **Approved in 2012 for long-term weight management**
- **Mechanism:**
  - Phentermine: inhibits NE and dopamine release
  - Topiramate: mechanism on weight loss is not known
  - Increases satiety – appetite suppressant
Phentermine-topiramate (Qsymia)

Efficacy: 10.7 kg mean weight loss beyond that achieved by placebo (12.6 kg vs. 1.9 kg) at one year (Phase 3 RCT; *Obesity* (2012); 202, 330–342)

Adverse effects: tachycardia, insomnia, paresthesias, dizziness, distorted taste sensation, constipation, dry mouth, anxiety, suicidality (rare), acute angle closure glaucoma (rare), metabolic acidosis (rare), increased serum creatinine (rare)

Contraindications: pregnancy, glaucoma, hyperthyroidism, MAOIs, history of suicide attempt
Phentermine/Topiramate

- Combination gives greater effectiveness with fewer side effects
- Cost: $150.00/month
- Side effects: dry mouth, numbness, tingling, insomnia, dizziness, anxiety, irritability and disturbance in attention
Phentermine/Topiramate Phase III Trial

Gadde KM et al. Lancet. 2011;377(9774):1314-52
Topiramate/Phentermine (Qsymia) Effects on Weight

Lancet. 2011 Apr 16;377(9774):1341-52
Phentermine/Topiramate

- Risk of birth defects: women need pregnancy test on starting and monthly while using.
- Reduces blood pressure, glucose, insulin, triglycerides and raises HDL.
- Unclear if physicians will prescribe off label using generic phentermine and topiramate.
- Most effective medication available 10-12% weight loss.
Phentermine/Topiramate

- **Dosing:**
  - 3.25mg/23mg, 7.5mg/46mg, 11.25mg/69mg and 15mg/92mg.
  - Start at 3.75/23 mg daily x 2 weeks then ↑to 7.5/46 mg
  - After 12 weeks can ↑to 11.25/69mg

- **Cost:** $180/month
Naltrexone/Bupropion

- Recently FDA approved as Contrave
- CVD safety study in progress
- Mechanism:
  - Naltrexone: opioid receptor antagonist
  - Bupropion: NE/dopamine reuptake inhibitor
  - Appetite suppressant, reduces cravings?
- Adverse events: Nausea, headache, constipation, dizziness, vomiting, insomnia, dry mouth & hot flushes
Bupropion 360 & Naltrexone 32 mg

Placebo (N=511)  NB16 (N=471)  NB32 (N=471)

Placebo Completers (N=290)  NB16 Completers (N=284)  NB32 Completers (N=296)

ITT-LOCF

Observed

Completers

Placebo-subtracted weight loss
Week 56

Placebo-subtracted weight loss
Completers

P<0.001 for NB16 and NB32 vs. Placebo at all time points

Contrave: Bupropion and Naltrexone

24 Week Weight Loss (Completer Analysis)

Bupropion stimulates POMC neuron to release α-MSH, naltrexone blocks μ opiate receptor to prevents inhibition by Beta endorphin, thereby potentiating α-MSH release.

Source: Orexigen
Weight Loss With Naltrexone SR/Bupropion SR Combination Therapy as an Adjunct to Behavior Modification: The COR-BMOD Trial
# Naltrexone Bupropion

<table>
<thead>
<tr>
<th></th>
<th>Greenway et al.</th>
<th>Wadden et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 290)</td>
<td>NBSR 16 mg (n = 284)</td>
</tr>
<tr>
<td>Change in body weight (%)</td>
<td>–1.8%</td>
<td>–6.7%</td>
</tr>
<tr>
<td>Change in body weight (kg)</td>
<td>–1.9</td>
<td>–6.5</td>
</tr>
<tr>
<td>Participants with a weight loss of 5% or more</td>
<td>67 (23%)</td>
<td>155 (55%)</td>
</tr>
<tr>
<td>Participants with a weight loss of 10% or more</td>
<td>31 (11%)</td>
<td>85 (30%)</td>
</tr>
<tr>
<td>Participants with a weight loss of 15% or more</td>
<td>9 (3%)</td>
<td>40 (14%)</td>
</tr>
</tbody>
</table>
**Most Common Side Effects of Naloxone Bupropion**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Greenway et al.</th>
<th>Wadden et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 569)</td>
<td>NBSR 16 mg (n = 569)</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (5.3%)</td>
<td>155 (27.2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>53 (9.3%)</td>
<td>91 (16.9%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>32 (5.6%)</td>
<td>90 (15.8%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (2.6%)</td>
<td>44 (7.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (2.5%)</td>
<td>36 (6.3%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>11 (1.9%)</td>
<td>42 (7.4%)</td>
</tr>
</tbody>
</table>
Naltrexone Bupropion

- Dosing: 8 mg/90 mg tablets.
- Take one daily and titrate over three weeks to two bid.
- Cost: $40 – 220/month.
FDA approved 2014 as Saxenda.
- GLP-1 receptor agonist.
- Taper as tolerated over several weeks.
- CNS effect to promote satiety, slow GI emptying.
- Adverse effects: vomiting, diarrhea, constipation, low blood sugar, and increased appetite. Serious side effects can include pancreatitis, gallbladder disease, ATN (rare), and suicidality. It can also raise heart rate. Warning for ?medullary thyroid cancer
Liraglutide 3 mg/d in Obese Subjects

SCALE Obesity and Prediabetes: Efficacy of Liraglutide for Overweight/Obese Nondiabetic Subjects

- Phase 3a randomized, double-blind, placebo-controlled trial of 3,731 nondiabetic subjects with obesity and overweight with comorbidities
- Randomized 2:1 to liraglutide 3 mg (n=2,487) or placebo (n=1,244) plus calorie restriction, exercise
- Outcomes:
  - Weight loss at 56 weeks
  - Long-term efficacy of liraglutide 3 mg to delay type 2 diabetes onset in subjects with prediabetes

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Liraglutide (mean)</th>
<th>Placebo (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>40%</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21%</td>
<td>9%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Liraglutide 3 mg is an investigational agent; not FDA approved in the United States to treat overweight/obesity.

SCALE-Diabetes: Impact of Liraglutide on Weight Loss & Health-Related Quality of Life in Obesity/Overweight

- N=846 overweight or obese subjects with type 2 diabetes
- Randomized to liraglutide 3 mg, liraglutide 1.8 mg, or placebo plus calorie restriction, exercise
- Outcomes:
  - Weight loss at 56 weeks
  - Health-related quality of life improved with liraglutide 3 mg but not 1.8 mg

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Liraglutide 3 mg</th>
<th>Liraglutide 1.8 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>33%</td>
<td>31%</td>
<td>14%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26%</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Constipation</td>
<td>16%</td>
<td>10%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Liraglutide 3 mg is an investigational agent; not FDA approved in the United States to treat overweight/obesity. Liraglutide 1.8 mg is not FDA approved in the United States to treat overweight/obesity.
Liraglutide 3.0 mg

- **Dosing:** 0.6 mg SC once daily.
  - Titrate by 0.6 mg each week up to 3.0 mg daily.
  - Hold or reduce dose if nausea develops.

- **Cost:** not in pharmacies yet.
- **Victoza** costs $650/month, but is often covered by insurance when used to treat diabetes.
# Efficacy of Currently Available Weight Loss Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Average Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>3.6% &gt; placebo</td>
</tr>
<tr>
<td>Orlistat</td>
<td>2.75% &gt; placebo</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>3.3% &gt; placebo</td>
</tr>
<tr>
<td>Phentermine/Topiramate</td>
<td>9% &gt; placebo</td>
</tr>
<tr>
<td>Naltrexone/Bupropion</td>
<td>8.1% &gt; placebo</td>
</tr>
<tr>
<td>Liraglutide 3 mg</td>
<td>5.4% &gt; placebo</td>
</tr>
</tbody>
</table>
Dietary supplements and herbal medications

- Chromium picolote
- Chitosan
- Conjugated linoleic acid
- Ephedra alkaloids (Ma Huang)
- Garcinia cambogia

"Herbal medications are not recommended as part of a weight loss program. They have unpredictable amounts of active ingredients and unpredictable – and potentially harmful – side effects.”

www.NHLBI.NIH.gov
Zonisamide 360 + Bupropion 360 mg
Weight Loss at 1 Year of Treatment

Placebo controlled weight loss through 24 weeks
Assist
Establish Appropriate Intervention

- Therapeutic Lifestyle Change (TLC)
- Pharmacotherapy
- Surgery
Current Surgical Therapy of Obesity

- **Procedures: 3 Types**
  - **Restrictive**
    - Vertical Banded Gastroplasty
    - Lap Adjustable Gastric Band
    - Sleeve Gastrectomy
  - **Restrictive and Malabsorptive**
    - Roux en Y Gastric Bypass
  - **Malabsorptive**
    - Duodenal Switch
    - Biliopancreatic Diversion
Swedish Obese Subjects (SOS) Study: Surgical Treatment Followed for 10 years

Weight Change (%)

Years of Follow-up


Slide from Fujioka K, @ http://www.medscape.com/viewprogram/8637
Thank you!