Emerging Therapies in Treatment of Obesity

The Endocannabinoid System (ECS)

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Preceptor: James Weems, RPh

Pharmacotherapy Rounds
January 14, 2011

Objectives:
1. Review current pharmacologic therapies for obesity treatment
2. Discuss pharmacological agents used in the treatment of obesity without approval
3. List pharmacological agents in clinical trials for treatment of obesity
4. Explain the endocannabinoid system and its purpose in obesity treatment
5. Evaluate and summarize clinical trial data for the cannabinoid receptor-1 antagonist

I. What is Obesity?
   A. Figure 1
   
<table>
<thead>
<tr>
<th>Weight status</th>
<th>Body mass index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Healthy weight</td>
<td>18.5–24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–29.9</td>
</tr>
<tr>
<td>Obesity class I</td>
<td>30–34.9</td>
</tr>
<tr>
<td>Obesity class II</td>
<td>35–39.9</td>
</tr>
<tr>
<td>Obesity class III</td>
<td>≥40</td>
</tr>
</tbody>
</table>


   B. Figure 2
   
<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMI category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, exercise, behavior therapy</td>
<td>25–26.9</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>27–29.9</td>
</tr>
<tr>
<td>Surgery</td>
<td>30–35</td>
</tr>
<tr>
<td></td>
<td>35–39.9</td>
</tr>
<tr>
<td></td>
<td>≥40</td>
</tr>
</tbody>
</table>


   C. Figure 3

\[
\text{BMI} = \frac{\text{Weight in Pounds}}{(\text{Height in inches}) \times (\text{Height in inches})} \times 703
\]

or

\[
\text{BMI} = \frac{\text{Weight in Kilograms}}{(\text{Height in Meters}) \times (\text{Height in Meters})}
\]

II. How Does Obesity Affect the U.S?
   A. Healthy People 2010 set a national goal of 15% obesity prevalence for adults in each state. (1)
   1. Healthy People 2010 provides science based objectives for improving all American’s health. (1)
   
   B. 2009 data from the CDC self-reported survey found 26.7% of the U.S. population is obese. (2)
   
   C. Prevalence ranged from 18.6% to 34.4% (2)
   1. Lowest prevalence—Colorado (18.6%) and District of Columbia (19.7%)
   2. 9 states had obesity prevalence higher than 30%
   3. Highest prevalence—Mississippi (34.4% (See Appendix A)
   4. Demographic characteristics show age 50-59, black (non-Hispanic), less than high school graduate and the south region had the highest Prevalence of obesity. (See Appendix B)

III. What Complications Arise from Obesity? (See Appendix C) (3, 4)
   A. Sex hormone imbalance
   1. Cancer
   
   B. Increased fatty acids
   1. Diabetes
   2. Hypertension
   3. Heart disease
   
   C. Mechanical stress
   1. Sleep apnea

IV. Pharmacotherapy
   A. Pharmacotherapy is based on the concept of providing a sustained negative energy (calorie) balance (5)
   
   B. Mechanisms for treating obesity
   1. Centrally to suppress appetite (5)
      a. Appetite-suppressing drugs or anorexiants
      b. Lessens hunger but increases satiation and satiety
      c. Ultimate reduction caloric intake
      d. Act at ventromedial and later hypothalamic regions in the CNS
   2. Peripherally to block the absorption of fat (5)
      a. Lipase inhibitor
      b. Reversible inhibitor of enzymes responsible for hydrolysis of dietary fat
      c. Prevents digestion and absorption of 30% of dietary fat
      d. Acts in the lumen of the stomach and small intestine
   3. Selective blockade of the endocannabinoid system
C. Modest reductions of 5-10% of body weight will improve lipid profile, insulin sensitivity and endothelial function, reduce thrombosis and inflammatory markers. (6)

D. Very few drugs are approved for treatment of obesity (7)
   1. FDA requires >10% reduction in body weight for weight loss to be significant.

V. Approved agents for treatment of obesity (8)
   A. Classical sympathomimetic adrenergic agents
      1. Benzphetamine (Didrex ®)
      2. Phendimetrazine (Bonril®)
      3. Diethylproprion (Tenuate®)
      4. Phentermine (Adipex-P ®)
   B. Lipase Inhibitor
      1. Orlistat (Xenical® or Alli®)

VI. Other agents used for treatment of obesity
   A. Fluoxetine (Prozac®) and Setraline (Zoloft®) (7, 9)
      1. Selective serotonin reuptake inhibitors; block serotonin transporters; prolong the action of serotonin; reduce food intake
      2. 60 mg/d of fluoxetine three times daily
   B. Bupropion (Wellbutrin®) (6-9)
      1. Norepinephrine and dopamine reuptake inhibitor
      2. 300-400 mg/d twice daily
   C. Topiramate (Topamax®) (7, 9)
      1. Weak carbonic anhydrase inhibitor; modulates effects at GABA receptors (thought to reduce food intake) and AMPA glutamate receptor; blockage of Na+ or Ca++ channels
      2. 100-200 mg/d (taken twice daily)
   D. Zonisamide (Zonegram®) (6-9)
      1. Serontonergic and dopaminergic activity in addition to inhibiting sodium and calcium channels
      2. 100-600 mg/d
   E. Lamotrigine (Lamictal®) (7, 9)
      1. 25 mg-200 mg per day over 6 week increase
   F. Metformin (Glucophage®) (7, 9)
      1. Reduces hepatic glucose production; decreases intestinal absorption form GI tract; enhances insulin sensitivity
      2. 850 mg twice daily
   G. Pramlintide (Symlin®) (7, 9)
      1. Synthetic amylin (peptide found in beta cells of pancreas) analog
      2. 60-120 mcg before major meals
   H. Exenatide (Byetta®) (7, 9)
1. Decreases food intake; decreases body weight; slows gastric emptying; decreases food intake by 19%
2. 5-10 mcg SQ twice daily 1 hour prior to main meals. 6 hours apart

VII. Agents removed from the market
A. Sibutramine (Meridia®) (10)
   1. Serotonin and norepinephrine reuptake inhibitor with no abuse potential
   2. FDA recommending against use of and prescribing
   3. SCOUT trial showed a 16% increase in risk of cardiovascular events in sibutramine treated patients
      a. Non-fatal heart attack
      b. Non-fatal stroke
      c. Resuscitation after cardiac arrest
      d. Cardiovascular death
   4. FDA concluded the risk of sibutramine did not outweigh the modest weight loss seen
   5. Abbott has stopped marketing sibutramine in the US as of October 2010

VIII. Investigational agents for treatment of obesity
A. Neuropeptide Y Receptor Antagonists (8)
   1. Proposed to decrease food intake
   2. Increase energy expenditure
   3. Decrease body weight by deactivating receptors in the hypothalamus
B. Serotonin 2C Receptor Agonists (8)
   1. Lorcaserin has phase II clinical trial data
   2. HT-2C receptor agonists suppress food intake
C. Cetilistat (8)
   1. A pancreatic Lipase Inhibitor
   2. Mean weight loss after 12 weeks 4.32 kg
D. Rimonabant (Acomplia®) (6-9, 12)
   1. Cannabinoid Receptor-1 antagonist

IX. The Endocannabinoid System (12-14)
A. Began with observation that marijuana caused hunger
B. Signaling network that regulates appetite and metabolism
C. This system is overstimulated by:
   1. Weight gain
   2. Abdominal fast mass gain
   3. Consumption of high-fat/high-calorie diet
D. Cannabinoid receptor-1 (12-14)
   1. Primarily modulates food intake and energy expenditure
   2. Located in the CNS
   3. Located in peripheral tissues
      a. Adipocytes (fat cells that secrete proteins (adipokines))
i. Influence weight regulation, vascular integrity, inflammation and disease
b. Hepatocytes
c. Skeletal muscle
d. Endothelial cells
e. Gastrointestinal Tract
X. Rimonabant in Obesity Trials
   A. RIO—Lipids (14, 15)


<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess the effect of 12 months of randomized double-blind treatment with rimonabant at a dose of 5 or 20 mg, as compared with placebo, in addition to hypocaloric diet, on the loss of the body weight in patients who are overweight or obese, have untreated dyslipidemia, and do not have diabetes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>67 sites in 8 countries Randomized, double-blind treatment with placebo or rimonabant at a dose of 5 or 20 mg</td>
</tr>
<tr>
<td>Patient Population</td>
<td>18-70 years of age; BMI of 27-40; fasting plasma TG level of 150-700; ration of TC:HDL higher the 5 (men) 4.5 (women); variation of bodyweight within previous 3 months of less than 5 kg Exclusion Criteria See Appendix G</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Weight loss; reduction in waist circumference; increase in HDL cholesterol; reduction in TG; increase in plasma adiponectin levels</td>
</tr>
<tr>
<td>Intervention and methods</td>
<td>1036 patients were stratified according to baseline TG and weight loss during run in period in a 1:1:1 ratio of placebo, 5mg/d or 20mg/d rimonabant. Follow up visits were every 2 weeks for first 2 visits, then monthly for 12 months. (body weight, blood pressure, waist circumference, smoking status and concomitant medications were assessed at each visit)</td>
</tr>
<tr>
<td>Results</td>
<td>40% of patients in each group dropped out of the 12-month study (mostly to do adverse event in 20mg/d group Weight loss &gt;5% was 19.5% in placebo vs. 58.4% in 20mg/d Weight loss &gt;10% was 7.2% in placebo vs. 32.6% in 20mg/d Weight loss occurred in first 9 months of study and maintained throughout the 12 months. TG fell 15-38% in 20mg/d rimonabant group HDL increases were dose dependent No change was observed in LDL Plasma adiponectin levels increased by 57.7% with</td>
</tr>
<tr>
<td>Author’s Conclusion</td>
<td>Rimonabant significantly reduces body weight and waist circumference and improves the profile of several metabolic risk factors in high-risk patients who are over-weight or obese and have atherogenic dyslipidemia.</td>
</tr>
<tr>
<td>Comments</td>
<td>This study doesn’t explain what the initial run-in period consisted of and doesn’t account for its affect on the total weight loss from baseline. Weight loss was generally greater in patients who completed the study.</td>
</tr>
</tbody>
</table>
### B. RIO—Diabetes (14, 17)

<table>
<thead>
<tr>
<th><strong>Scheen, AJ; Finer, N; Hollander, P; Jensen, MD; et al. Efficacy and Tolerability of Rimonabant in Overweight or Obese Patients With Type 2 Diabetes: A Randomized Controlled Study. Lancet: 2006;368:1660-1672</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
</tr>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
</tr>
<tr>
<td><strong>Intervention and methods</strong></td>
</tr>
<tr>
<td><strong>Results</strong></td>
</tr>
<tr>
<td><strong>Author’s Conclusion</strong></td>
</tr>
<tr>
<td><strong>Comments</strong></td>
</tr>
</tbody>
</table>
## Emerging Therapies in Treatment of Obesity

### C. RIO—North America (14, 18)

<table>
<thead>
<tr>
<th>Pi-Sunyer, FX; Aronne, LJ; Heshmati, HM; Devin, J; et al. Effects of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients. JAMA 2006;295:761-775</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Objective</th>
<th>To compare the efficacy and safety of rimonabant with placebo each in conjunction with diet and exercise for sustained changes in weight and cardiometabolic risk factors over 2 years.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Design</th>
<th>Multi-centered (64 US and 8 Canadian Clinics), randomized, double blind placebo controlled clinical trial</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>3045 patients who are obese ≥ 30 or overweight &gt; 27 with HTN or dyslipidemias; 18 years or older. Exclusion criteria: body weight fluctuation of more than 5 kg in previous 3 months; clinically significant cardiac, renal, hepatic, GI, neuro-psychiatric or endocrine disorders; drug treated or diagnosed T1DM/T2DM; use of weight/appetite altering medications; history or current substance abuse; previous 6 month change in smoking habits Women of childbearing age used approved medical contraception</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Body Weight change over 1 year and prevention of weight regain during year 2; waist circumference, plasma lipid levels, cardiometabolic risk factors</th>
</tr>
</thead>
</table>

| Intervention and Methods | 1. 4 week placebo plus diet
2. Patients who completed 1st 4 weeks were randomized (1:2:2) to placebo, 5mg rimonabant and 20 mg rimonabant for 1 year
3. Patients in rimonabant groups were rerandomized to placebo or the same dosage from previous randomization for 1 year (Appendix H)
Each study-site IRB approved the trial separately. |
|---|---|

| Results | ~50% of patients in each group finished year 1; ~70% of patients who finished year 1 finished year 2
20mg/d rimonabant produced greater reduction in weight, waist circumference and TG level; increases in HDL
Patients switched to placebo from rimonabant experienced weight regain vs. those who continued 20mg/d rimonabant maintained weight loss |
|---|---|

<table>
<thead>
<tr>
<th>Author’s Conclusion</th>
<th>Results suggest that 20mg/d of rimonabant effectively reduces body weight and waist circumference and also improves several cardiometabolic risk factors.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Comments</th>
<th>Attrition rate was very high in this study, but it is common among weight loss studies. Results were dose dependent. Clinically significant weight loss from year 1 was maintained during both years in patients receiving 20m/d of rimonabant</th>
</tr>
</thead>
</table>
D. RIO—EUROPE (14, 19)


<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess efficacy and safety of rimonabant in reducing body weight and improving cardiovascular risk factors in overweight or obese patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>2 year; placebo controlled; randomized double blind treatment study Multicenter (60 sites from Europe and 20 sites from US)</td>
</tr>
<tr>
<td>Patient Population</td>
<td>1507 who are obese ≥ 30 or overweight &gt; 27 with HTN or dyslipidemias Men or women 18 years or older Exclusion criteria: less than 5 kg variation of weight within 3 months; substantial endocrine disease, diabetes mellitus, cardiovascular, pulmonary disease, hepatic, renal, neurological or psychological disorders; depression requiring hospitalization, 2 or more recurrent episodes of depression or suicide attempt; history surgical procedures for weight loss; intention to stop smoking and concomitant use of medications known to alter body weight or appetite</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Primary: weight change form baseline after 1 year Secondary: waist circumference, concentrations of glucose and insulin, fasting HDL, TG and prevalence of metabolic syndrome</td>
</tr>
<tr>
<td>Intervention and methods</td>
<td>2 week screening period; 4 week single blind run it period Randomized in 1:2:2 ratio like RIO North America Patients were seen every 14 days for 1st month, then every 28 days until end of study Bodyweight, waist circumference, blood pressure were measured at every visit; lipid profile, fasting glucose and insulin were measured every 3 months</td>
</tr>
<tr>
<td>Results</td>
<td>61% of patients completed the study Change in bodyweight was significantly greater in rimonabant treated groups vs. placebo Frequency of adverse events was greater in 20mg/d group</td>
</tr>
<tr>
<td>Author’s Conclusion</td>
<td>Treatment with rimonabant over 1 year led to sustained clinically weight loss, reduction in waist circumference and associated improvements in several cardiovascular and metabolic risk factors</td>
</tr>
</tbody>
</table>

XI. Summary

A. The ECS show promise in treatment and maintenance of chronic obesity in patients with BMI>27.

B. Its side effect profile limits its approval status in the U.S.

C. Long term studies are needed to accurately identify risk vs. benefit with rimonabant.

*Body mass index (BMI) ≥30.0; BMI was calculated from self-reported weight and height (weight [kg] / height [m]^2).
### Table: Self-reported prevalence of obesity* among adults, by sex and selected characteristics — Behavioral Risk Factor Surveillance System, United States, 2009

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (N = 405,102)</th>
<th>Men (n = 158,455)</th>
<th>Women (n = 246,647)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>26.7 (26.4–27.0)</td>
<td>27.4 (26.9–27.8)</td>
<td>26.0 (25.7–26.4)</td>
</tr>
<tr>
<td><strong>Age group (yrs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–29</td>
<td>20.3 (19.5–21.2)</td>
<td>20.1 (18.8–21.4)</td>
<td>20.6 (19.5–21.7)</td>
</tr>
<tr>
<td>30–39</td>
<td>27.8 (27.1–28.6)</td>
<td>29.4 (28.2–30.7)</td>
<td>26.2 (25.3–27.1)</td>
</tr>
<tr>
<td>40–49</td>
<td>29.4 (28.6–30.1)</td>
<td>31.0 (30.0–32.0)</td>
<td>27.8 (27.0–28.6)</td>
</tr>
<tr>
<td>50–59</td>
<td>31.1 (30.6–31.7)</td>
<td>31.9 (31.1–32.8)</td>
<td>30.3 (29.6–31.0)</td>
</tr>
<tr>
<td>60–69</td>
<td>30.9 (30.3–31.5)</td>
<td>30.5 (30.1–31.3)</td>
<td>31.3 (30.6–32.1)</td>
</tr>
<tr>
<td>≥70</td>
<td>20.5 (20.0–21.0)</td>
<td>19.8 (19.0–20.5)</td>
<td>21.0 (20.4–21.6)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>25.2 (24.9–25.5)</td>
<td>27.1 (26.6–27.6)</td>
<td>23.3 (23.0–23.7)</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>36.8 (35.7–37.9)</td>
<td>30.9 (29.2–32.8)</td>
<td>41.9 (40.5–43.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>30.7 (29.5–31.9)</td>
<td>30.6 (28.7–32.5)</td>
<td>30.8 (29.4–32.2)</td>
</tr>
<tr>
<td>Other race</td>
<td>16.7 (15.5–18.0)</td>
<td>16.9 (15.2–18.8)</td>
<td>16.5 (15.0–18.1)</td>
</tr>
<tr>
<td><strong>Educational level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school graduate</td>
<td>32.9 (31.8–34.0)</td>
<td>29.6 (27.9–31.4)</td>
<td>36.4 (35.1–37.8)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>29.5 (29.0–30.1)</td>
<td>29.5 (28.6–30.4)</td>
<td>29.5 (28.9–30.2)</td>
</tr>
<tr>
<td>Some college</td>
<td>29.1 (28.6–29.7)</td>
<td>30.6 (29.6–31.5)</td>
<td>27.9 (27.2–28.5)</td>
</tr>
<tr>
<td>College graduate</td>
<td>20.8 (20.4–21.2)</td>
<td>22.9 (22.2–23.5)</td>
<td>18.6 (18.2–19.1)</td>
</tr>
<tr>
<td><strong>Census region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>24.3 (23.6–24.9)</td>
<td>25.2 (24.2–26.2)</td>
<td>23.4 (22.6–24.2)</td>
</tr>
<tr>
<td>Midwest</td>
<td>28.2 (27.7–28.7)</td>
<td>29.2 (28.4–30.1)</td>
<td>27.2 (26.5–27.9)</td>
</tr>
<tr>
<td>South</td>
<td>28.4 (27.9–29.0)</td>
<td>28.8 (28.0–29.7)</td>
<td>28.1 (27.5–28.7)</td>
</tr>
<tr>
<td>West</td>
<td>24.4 (23.8–25.0)</td>
<td>25.1 (24.2–26.0)</td>
<td>23.7 (22.9–24.4)</td>
</tr>
</tbody>
</table>

* Body mass index (BMI) ≥ 30.0; BMI was calculated from self-reported weight and height (weight [kg] / height [m]²).

† Confidence interval.

9 Additional information available at https://www.census.gov.
Emerging Therapies in Treatment of Obesity

Appendix C (4):

Appendix D (23, 24):
Appendix E (6-9):

<table>
<thead>
<tr>
<th>Obesity Agents</th>
<th>Weight Loss Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine or Sertraline</td>
<td>Produced a 27% decrease in food intake in a 2 week placebo controlled study; weight loss was regained during 2nd 6 months of trial deeming inappropriate for long term usage</td>
</tr>
<tr>
<td>Bupropion</td>
<td>2.77 kg (6.1lbs) more weight loss than placebo</td>
</tr>
<tr>
<td>Topiramate</td>
<td>6.5% of baseline weight lost compared with placebo</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>5% of baseline weight lost compared with placebo</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>5.2 kg more weight loss compared with placebo</td>
</tr>
<tr>
<td>Metformin</td>
<td>DPP trial shows 2.5% loss in bodyweight compared with placebo BIGPRO study showed a 1-2 kg weight reduction compared with placebo</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>1.7 kg more weight loss than placebo</td>
</tr>
<tr>
<td>Exetanide</td>
<td>2.7-2.9 kg weight loss in diabetes patients during diabetic trials</td>
</tr>
</tbody>
</table>
Emerging Therapies in Treatment of Obesity

Appendix F (14):

a. Excess food intake - obesity
   Overactivity of the EC system
   → Brain
   → ?
   → Gastrointestinal
   → ↑ Food intake
   → Genetic susceptibility?
   → ↑ Abdominal adiposity

Liver
- ↑ Lipogenesis
- ↑ Liver fat
- ↑ Glucose production
- ↓ Insulin degradation

Adipocytes
- ↑ Adiponectin
- TNF-α
- IL-6
- ↑ LPL
- ↑ Lipogenesis
- ↑ VLDL
- ↑ Insulinemia
- ↑ Apo A1 synthesis
- Glucose intolerance

Skeletal muscle?
- ↑ FFA

Impaired insulin action

b. Excess food intake - obesity
   Overactivity of the EC system
   → Brain
   → ↓ Food intake
   → Genetic susceptibility?
   → ↑ Abdominal adiposity

Liver
- ↓ Lipogenesis
- ↓ Liver fat
- ↓ Glucose production
- ↑ Insulin degradation

Adipocytes
- ↓ Adiponectin
- TNF-α
- IL-6
- ↓ LPL
- ↓ Lipogenesis
- ↓ VLDL
- ↓ Insulinemia
- ↑ Apo A1 synthesis
- Improved glucose intolerance

Skeletal muscle?
- ↓ FFA

Rimonabant

Improved insulin action

• Increased waist (abdominal obesity)
• Insulin resistance
• High triglyceride-low HDL cholesterol dyslipidemia
• Inflammatory profile

↑ Risk of CVD and type 2 diabetes

• Decreased waist (abdominal obesity)
• Improved insulin sensitivity and glucose tolerance
• ↓ Triglycerides and ↑ HDL cholesterol
• Reduced inflammation

↑ Risk of CVD and type 2 diabetes
Appendix G (14, 15):

<table>
<thead>
<tr>
<th>Exclusion Criteria RIO-Lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of pharmacologic treatment for dyslipidemia within 6 weeks before screening</td>
</tr>
<tr>
<td>Treatment with very low calorie diet within 6 months before screening</td>
</tr>
<tr>
<td>Clinically significant cardiovascular, endocrine, pulmonary, neurologic, psychiatric, gastrointestinal, hepatic, renal, hematologic, renal, or dermatologic disease</td>
</tr>
<tr>
<td>Abnormal thyrotropin</td>
</tr>
<tr>
<td>History of marijuana or hashish use</td>
</tr>
<tr>
<td>Treatment of epilepsy, eating disorder or malignant disease within 5 years</td>
</tr>
<tr>
<td>Pregnancy or lactation</td>
</tr>
<tr>
<td>Recently quit smoking or considering quitting</td>
</tr>
</tbody>
</table>

Appendix H (14, 18):
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