Obesity and Its Impact on the Gastrointestinal Tract

Grand Rounds
By: Amy Tiu
Objectives: Highlight the Impact of Obesity

- Esophageal Disease
- Irritable Bowel Syndrome
- Biliary Disease
- Gastrointestinal Cancer
- Liver and Pancreatic Transplant
- Inflammatory Bowel Disease
- Brief overview of Orlistat
Case

- 28 yo female presents with burning and epigastric pain for one year
- Reports started after the birth of her first child
- 5 feet 2 inches
- 220 pounds
Case: What is her BMI?

- Weight (kg)/ Ht (meters squared)
- Body Mass Index

The patient’s BMI = 40.2
## Body Mass Index

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4'10&quot;</td>
<td>91</td>
<td>96</td>
<td>100</td>
<td>105</td>
<td>110</td>
<td>115</td>
<td>119</td>
<td>124</td>
<td>129</td>
<td>134</td>
<td>138</td>
<td>143</td>
<td>148</td>
<td>153</td>
<td>158</td>
<td>162</td>
<td>167</td>
<td>172</td>
<td>177</td>
<td>181</td>
<td>186</td>
<td>191</td>
<td></td>
</tr>
<tr>
<td>5'</td>
<td>97</td>
<td>102</td>
<td>107</td>
<td>112</td>
<td>118</td>
<td>123</td>
<td>128</td>
<td>133</td>
<td>138</td>
<td>143</td>
<td>148</td>
<td>153</td>
<td>158</td>
<td>163</td>
<td>168</td>
<td>174</td>
<td>179</td>
<td>184</td>
<td>189</td>
<td>194</td>
<td>199</td>
<td>204</td>
<td></td>
</tr>
<tr>
<td>5'1&quot;</td>
<td>100</td>
<td>106</td>
<td>111</td>
<td>116</td>
<td>122</td>
<td>127</td>
<td>132</td>
<td>137</td>
<td>143</td>
<td>148</td>
<td>153</td>
<td>158</td>
<td>164</td>
<td>169</td>
<td>174</td>
<td>180</td>
<td>185</td>
<td>190</td>
<td>195</td>
<td>201</td>
<td>206</td>
<td>211</td>
<td></td>
</tr>
<tr>
<td>5'2&quot;</td>
<td>104</td>
<td>109</td>
<td>115</td>
<td>120</td>
<td>126</td>
<td>131</td>
<td>136</td>
<td>142</td>
<td>147</td>
<td>153</td>
<td>158</td>
<td>164</td>
<td>169</td>
<td>175</td>
<td>180</td>
<td>186</td>
<td>191</td>
<td>196</td>
<td>202</td>
<td>207</td>
<td>213</td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>5'3&quot;</td>
<td>107</td>
<td>113</td>
<td>118</td>
<td>124</td>
<td>130</td>
<td>135</td>
<td>141</td>
<td>146</td>
<td>152</td>
<td>158</td>
<td>163</td>
<td>169</td>
<td>175</td>
<td>180</td>
<td>186</td>
<td>191</td>
<td>197</td>
<td>203</td>
<td>208</td>
<td>214</td>
<td>220</td>
<td>225</td>
<td></td>
</tr>
<tr>
<td>5'4&quot;</td>
<td>110</td>
<td>116</td>
<td>122</td>
<td>128</td>
<td>134</td>
<td>140</td>
<td>145</td>
<td>151</td>
<td>157</td>
<td>163</td>
<td>169</td>
<td>174</td>
<td>180</td>
<td>186</td>
<td>192</td>
<td>197</td>
<td>204</td>
<td>209</td>
<td>215</td>
<td>221</td>
<td>227</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>5'5&quot;</td>
<td>114</td>
<td>120</td>
<td>126</td>
<td>132</td>
<td>138</td>
<td>144</td>
<td>150</td>
<td>156</td>
<td>162</td>
<td>168</td>
<td>174</td>
<td>180</td>
<td>186</td>
<td>192</td>
<td>198</td>
<td>204</td>
<td>210</td>
<td>216</td>
<td>222</td>
<td>228</td>
<td>234</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>5'6&quot;</td>
<td>118</td>
<td>124</td>
<td>130</td>
<td>136</td>
<td>142</td>
<td>148</td>
<td>155</td>
<td>161</td>
<td>167</td>
<td>173</td>
<td>179</td>
<td>186</td>
<td>192</td>
<td>198</td>
<td>204</td>
<td>210</td>
<td>216</td>
<td>222</td>
<td>229</td>
<td>235</td>
<td>241</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td>5'7&quot;</td>
<td>121</td>
<td>127</td>
<td>134</td>
<td>140</td>
<td>146</td>
<td>153</td>
<td>159</td>
<td>166</td>
<td>172</td>
<td>178</td>
<td>185</td>
<td>191</td>
<td>198</td>
<td>204</td>
<td>211</td>
<td>217</td>
<td>223</td>
<td>230</td>
<td>236</td>
<td>242</td>
<td>249</td>
<td>255</td>
<td></td>
</tr>
<tr>
<td>5'8&quot;</td>
<td>125</td>
<td>131</td>
<td>138</td>
<td>144</td>
<td>151</td>
<td>158</td>
<td>164</td>
<td>171</td>
<td>177</td>
<td>184</td>
<td>190</td>
<td>197</td>
<td>203</td>
<td>210</td>
<td>216</td>
<td>223</td>
<td>230</td>
<td>236</td>
<td>243</td>
<td>249</td>
<td>256</td>
<td>262</td>
<td></td>
</tr>
<tr>
<td>5'9&quot;</td>
<td>128</td>
<td>135</td>
<td>142</td>
<td>149</td>
<td>155</td>
<td>162</td>
<td>169</td>
<td>176</td>
<td>182</td>
<td>189</td>
<td>196</td>
<td>203</td>
<td>209</td>
<td>216</td>
<td>223</td>
<td>230</td>
<td>236</td>
<td>243</td>
<td>249</td>
<td>256</td>
<td>262</td>
<td>269</td>
<td></td>
</tr>
<tr>
<td>5'10&quot;</td>
<td>132</td>
<td>139</td>
<td>146</td>
<td>153</td>
<td>160</td>
<td>167</td>
<td>174</td>
<td>181</td>
<td>188</td>
<td>195</td>
<td>202</td>
<td>209</td>
<td>216</td>
<td>222</td>
<td>229</td>
<td>236</td>
<td>243</td>
<td>250</td>
<td>257</td>
<td>264</td>
<td>271</td>
<td>278</td>
<td></td>
</tr>
<tr>
<td>5'11&quot;</td>
<td>136</td>
<td>143</td>
<td>150</td>
<td>157</td>
<td>164</td>
<td>171</td>
<td>178</td>
<td>186</td>
<td>193</td>
<td>200</td>
<td>208</td>
<td>215</td>
<td>222</td>
<td>229</td>
<td>236</td>
<td>243</td>
<td>250</td>
<td>257</td>
<td>265</td>
<td>272</td>
<td>279</td>
<td>286</td>
<td></td>
</tr>
<tr>
<td>6'</td>
<td>140</td>
<td>147</td>
<td>154</td>
<td>162</td>
<td>169</td>
<td>177</td>
<td>184</td>
<td>191</td>
<td>199</td>
<td>206</td>
<td>213</td>
<td>221</td>
<td>228</td>
<td>235</td>
<td>242</td>
<td>250</td>
<td>258</td>
<td>265</td>
<td>272</td>
<td>279</td>
<td>287</td>
<td>294</td>
<td></td>
</tr>
<tr>
<td>6'1&quot;</td>
<td>144</td>
<td>151</td>
<td>159</td>
<td>166</td>
<td>174</td>
<td>182</td>
<td>189</td>
<td>197</td>
<td>204</td>
<td>212</td>
<td>219</td>
<td>227</td>
<td>235</td>
<td>242</td>
<td>250</td>
<td>257</td>
<td>265</td>
<td>272</td>
<td>280</td>
<td>288</td>
<td>295</td>
<td>302</td>
<td></td>
</tr>
<tr>
<td>6'2&quot;</td>
<td>148</td>
<td>155</td>
<td>163</td>
<td>171</td>
<td>179</td>
<td>186</td>
<td>194</td>
<td>202</td>
<td>210</td>
<td>218</td>
<td>225</td>
<td>233</td>
<td>241</td>
<td>249</td>
<td>256</td>
<td>264</td>
<td>272</td>
<td>280</td>
<td>287</td>
<td>295</td>
<td>303</td>
<td>311</td>
<td></td>
</tr>
<tr>
<td>6'3&quot;</td>
<td>152</td>
<td>160</td>
<td>168</td>
<td>176</td>
<td>184</td>
<td>192</td>
<td>200</td>
<td>208</td>
<td>216</td>
<td>224</td>
<td>232</td>
<td>240</td>
<td>248</td>
<td>256</td>
<td>264</td>
<td>272</td>
<td>279</td>
<td>287</td>
<td>295</td>
<td>303</td>
<td>311</td>
<td>319</td>
<td></td>
</tr>
<tr>
<td>6'4&quot;</td>
<td>156</td>
<td>164</td>
<td>172</td>
<td>180</td>
<td>189</td>
<td>197</td>
<td>205</td>
<td>213</td>
<td>221</td>
<td>230</td>
<td>238</td>
<td>246</td>
<td>254</td>
<td>263</td>
<td>271</td>
<td>279</td>
<td>287</td>
<td>295</td>
<td>304</td>
<td>312</td>
<td>320</td>
<td>328</td>
<td></td>
</tr>
</tbody>
</table>
Case: Why is she obese?
Is it what she ate?

- No regular exercise
- No regular diet
- 582 kcal 38.7 grams of fat
## BMI-associated Disease Risk

<table>
<thead>
<tr>
<th>Obesity Class</th>
<th>BMI (kg/m²)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>Increased</td>
</tr>
<tr>
<td>Normal</td>
<td>18.5 - 24.9</td>
<td>Normal</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 - 29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obesity I</td>
<td>30.0 – 34.9</td>
<td>High</td>
</tr>
<tr>
<td>Obesity II</td>
<td>35.0 – 39.9</td>
<td>Very High</td>
</tr>
<tr>
<td>Obesity III</td>
<td>≥ 40.0</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>

Additional risks: (1) waist circumference > 40 inches in men and >35 inches in women; (2) weight gain of > 5 kg since age 18-20 years; (3) poor aerobic fitness; and (4) Southeast Asian descent.

Gastroesophageal Reflux Disease (GERD)

- Relationship with obesity still not clear, but most studies find a strong association
- In the U.S., accepted as an independent risk factor for the presence of GERD
- Obesity is a risk factor that can identify patients with GERD who are at greatest risk for developing gastroesophageal junction adenocarcinoma
Gastroesophageal Reflux Disease (GERD)

A study of 65,363 adults in Sweden, found that obese subjects had a 3.5 fold increased risk of heartburn (independent of age, gender, and smoking p<0.001)

Manometric abnormalities in the morbidly obese

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defective LES</td>
<td>10 (16%)</td>
</tr>
<tr>
<td>Hypertensive LES</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Diffuse esophageal spasm</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Nutcracker esophagus</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Ineffective esophageal disorder</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Nonspecific esophageal disorder</td>
<td>14 (23%)</td>
</tr>
</tbody>
</table>
Esophageal motility

- Conflicting data
- A three year study of 111 morbidly obese patients demonstrated no correlation with BMI and lower esophageal sphincter pressure

## Esophageal Motility

<table>
<thead>
<tr>
<th></th>
<th>Obese (BMI=44)</th>
<th>Control (BMI=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower Esophageal</strong></td>
<td>11.9 +/- 5.3</td>
<td>15.9 +/- 2.7</td>
</tr>
<tr>
<td><strong>Sphincter Pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Why is there conflicting data for obesity and gastroesophageal disease?

- Symptoms may not reflect abnormalities
- Symptoms may be functional, null of any objective findings
- Patient who are obese may have a tendency to deny symptoms as part of behavioral tendencies toward eating despite discomfort
Obesity and Irritable Bowel Syndrome

Fig. 3. The prevalence of gastrointestinal symptoms associated with obesity collapsed over binge groups. The relative risk of each symptom is shown in parentheses. The asterisk (*) represents a significant $\chi^2$ statistic at the 0.05 level.

Obesity and Irritable Bowel Syndrome

- Fifty-eight twin pairs discordant for symptoms associated with irritable bowel syndrome (IBS) were evaluated.
- Significant association between IBS and obesity (OR=2.6; CI 1.0-6.4)
- May represent a familial-environmental influence on IBS

Obesity and Irritable Bowel Syndrome

- Etiology of the association with obesity unclear
- In 1994, Crowell et al. examined gastrointestinal symptoms in obese, obese binge eaters, normal, and normal obese binge eaters
Obesity and Irritable Bowel Syndrome

- Obesity was associated with more frequent constipation, diarrhea, straining, and flatus, whether or not subjects reported binge eating.
- Indigestion was more prevalent in both obese groups.

What if you are obese and binge eat?

First, binge eating has been defined by the Eating Disorders Work Group and DSM-IV:

- Eating in a discrete period of time an amount of the definitely larger than most
- A sense of lack of control over eating during the episode
- At least 3 of behavioral indicators
What if you are obese and binge eat?

- Binge eating has been defined by the Eating Disorders Work Group and DSM-IV
  (continued)
  - Marked distress regarding the binge
  - Two episodes a week for 6 months
  - Person does not fit criteria for bulimia nervosa or does not abuse medications
What if you are obese and binge eat?

Fig. 1. The average number (mean ± SE) of upper and lower gastrointestinal symptoms reported by each group. The asterisk (*) indicates significance at the $p < 0.05$ level.
Obesity and Gastrointestinal Tract Symptoms

In a cohort study in Australia (n=777), a regression model adjusting for sex, education, smoking, alcohol and all gastrointestinal symptoms, older age, less early satiety, increased stool frequency, and heartburn were all independently associated with increasing BMI (all p<0.01)

Obesity, IBS, & GI symptoms

- Evidence of an association between obesity and IBS
- Evidence that obesity associated with chronic gastrointestinal symptoms that may not fit definition of IBS but affect daily life of patients
Sixty percent of morbidly obese individuals undergoing gastric bypass surgery have gallbladder pathology.

Obesity and cholelithiasis

The Nurses Health Study demonstrated that, compared to lean women, obese women had a two-fold excess risk of symptomatic gallstones; and extremely obese women had a seven-fold excess risk of symptomatic gallstones.

Ten year follow-up of men in the Health Professionals study found an increased risk of cholelithiasis with severity of overweight.

Obesity and Biliary disease

- Risk of developing cholelithiasis increases with BMI in both genders.
- Unfortunately, risk of developing gallstones increases with weight loss.
- Risk factors for new formation of cholelithiasis include:
  - Weight loss rate 1.5 kg per week
  - Very low calorie diet with no fat content
## Risk of new gallstones

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low calorie diet for 8 to 16 weeks</td>
<td>10-12%</td>
</tr>
<tr>
<td>Gastric bypass Within 12-18 months Post –op</td>
<td>&gt;30%</td>
</tr>
</tbody>
</table>

One third of these stones formed were found to be asymptomatic

Erlinger, S., Gallstones in obesity and weight loss. Eur J Gastroenterol Heptol 2000.12 (12) 1347-52
Mechanisms for increased cholelithiasis after rapid weight loss

- Bile lithogenicity increases by decreased synthesis of bile acids and impaired gallbladder motility because of inadequate fat stimulation.

- This may also be combined with increased gallbladder secretion of mucin and calcium, as well as increased E2 prostaglandins and arachidonic acid.

Prevention of Cholelithiasis in an obese patient trying to lose weight

During rapid weight loss from a very low calorie diet with a high fat composition (577 kcal with 12 gm of fat) for 6 months; the high fat intake could prevent gallstone formation, probably by maintaining an adequate gallbladder emptying, which could counterbalance lithogenic mechanisms during weight loss.

Rough example of 577 kcal and 12 grams of fat

1 plain chick fil a sandwich (410 kcal and 16 gm fat)
1 regular Coca cola (140 kcal and 0 gm fat)
0.25 piece of a Pilsbury cookie
Prevention of Cholelithiasis in an obese patient trying to lose weight

- Increasing physical activity lowers biliary cholesterol levels and reduces gallstone disease in obese individuals.
  

- Orlistat added to a hypocaloric diet may protect overweight individuals from developing gallstones when they diet.
  
Obesity and Biliary disease

Torgerson et al
In a study of 6328 obese patients and 1125 randomly selected reference individuals, there was an increased prevalence of gallstones, gallbladder disease, and pancreatitis in the obese.

Obesity and Biliary disease

Obesity has also been found to be a significant preoperative predictor of conversion to laparotomy in patients undergoing laparoscopic cholecystectomy. In some cases the trocars and instruments are too short.

Obesity and Pancreatitis

<table>
<thead>
<tr>
<th></th>
<th>Nonobese (BMI &lt; 30)</th>
<th>Obese (BMI ≥ 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure</td>
<td>28 (9.5)</td>
<td>3 (11.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>Patients with systemic</td>
<td>74 (25.2)</td>
<td>10 (38.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with local</td>
<td>82 (27.9)</td>
<td>18 (69.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with organ</td>
<td>43 (14.6)</td>
<td>4 (15.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>failures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality in patients</td>
<td>22 (51.1)</td>
<td>2 (50)</td>
<td>1.0</td>
</tr>
<tr>
<td>with organ failures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td>22 (7.5)</td>
<td>2 (7.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Ranson score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>206 (65)</td>
<td>15 (57.7)</td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>80 (24.1)</td>
<td>9 (34.6)</td>
<td>0.48</td>
</tr>
<tr>
<td>≥6</td>
<td>34 (10.9)</td>
<td>2 (7.7)</td>
<td></td>
</tr>
</tbody>
</table>

Association of Severe Pancreatitis, Complications, Ranson Signs, and Outcome in Obese and Nonobese Patients

Obesity and pancreatitis

- Regardless of cause, obesity increased severity of acute pancreatitis
- 9-13 times more likely if high waist to hip ratio or waist circumference
- Risk of peri-pancreatic/pancreatic necrosis increased 3 fold

Mery, C. et al., Android fat distribution as a predictor of severity in acute pancreatitis
Pancreatology. 2002;2:543-549
Obesity and Gastrointestinal Cancer

The proportion of all deaths from cancer that is attributable to overweight and obesity in the United States adults 50 years of age or older may be as high as 14 percent in men and 20 percent in women.
Obesity and Cancer

Under the assumption that the relationship with obesity and cancer causal, more than 90,000 deaths per year from cancer might be avoided if everyone in the adult population could maintain a body mass index of under 25 throughout life.

Esophageal and Gastric Cancer

- Increased risk of adenocarcinoma of esophagus by factor of 2-3 with increased body mass index (BMI)
- Increased risk of adenocarcinoma of gastric cardia especially in men
- Why? Reason unclear
Gallbladder Cancer

- Elevated risk for gallbladder cancer in women with increased BMI (>40) by a factor of two

- Why? Most likely associated with increased risk of cholelithiasis
Obesity and Pancreatic Cancer

- An established risk factor for pancreatic cancer
- Meta-analysis of 14 studies involving 6000 cases of pancreatic cancer estimated that the relative risk of developing pancreatic cancer was about 20% greater in patients with a BMI>30 compared to normal weight individuals.

Obesity and Pancreatic Cancer

Why? One suggested mechanism includes the notion that increased adiposity increases insulin resistance and hyperplasia of pancreatic beta cells. Perhaps also leading to expansion of other pancreatic cell populations leading to cancer.
Obesity and Hepatic Cancer

- Increased risk of hepatocellular cancer (HCC); May be again due to affects of adiposity leading to cirrhosis
- Increased risk of HCC-related mortality; Obese men have a five fold increased risk compared to men with normal BMI and HCC

Obesity and Colon Cancer

- Being overweight increases the incidence and lethality of colon cancer
- Why? Mechanism unclear
Obesity and Colon Cancer

In a study of 13,420 men and women who had participated in the First National Health and Nutrition Examination Survey, twenty-year follow-up demonstrated that the hazard ratio for colon cancer increased with BMI, and is 3-4 fold higher in obese individuals than in those with a normal BMI.

Figure 2. Summary of Mortality from Cancer According to Body-Mass Index for U.S. Women in the Cancer Prevention Study II, 1982 through 1998.

For each relative risk, the comparison was between women in the highest body-mass-index (BMI) category (indicated in parentheses) and women in the reference category (body-mass index, 18.5 to 24.9). Asterisks indicate relative risks for women who never smoked. Results of the linear test for trend were significant (P≤0.05) for all cancer sites.

Figure 1. Summary of Mortality from Cancer According to Body-Mass Index for U.S. Men in the Cancer Prevention Study II, 1982 through 1998.

For each relative risk, the comparison was between men in the highest body-mass-index (BMI) category (indicated in parentheses) and men in the reference category (body-mass index, 18.5 to 24.9). Asterisks indicate relative risks for men who never smoked. Results of the linear test for trend were significant (P≤0.05) for all cancer sites.

Obesity and GI organ transplant
Recipient obesity is a significant risk factor for decreased graft survival after almost all types of abdominal organ transplants.

Following liver transplantation in severely obese patients, there was a higher rate of wound infection and death attributed to multi-organ failure compared to patients with a BMI<35.

In liver transplants, donor obesity is associated with steatosis of the graft, which in turn is associated with a higher incidence of primary nonfunction.
Obesity and Pancreatic transplant

- Donor obesity also impacts outcomes
- 711 cadaver pancreas transplants were analyzed for outcomes
- BMI > 30 donor group, surgical infections and thrombosis were significantly higher
- Exact reason unclear, may be increased fat around pancreas and increased vascular disease in donor

Obesity and IBD

- 2065 obese and non-obese Crohn’s patients were studied
- Time of development of anoperineal abscess or fistula was shorter in obese patients
- Obese patients were more prone to develop an active disease requiring hospitalization

Obesity and IBD

- Obesity not a risk factor for Crohn’s
- Use of steroids not more frequent in obese patients
- Minority of Crohn’s patients obese
Anti-obesity medications: Using the GI tract
# Anti-obesity medications approved

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sibutramine</th>
<th>Orlistat</th>
</tr>
</thead>
</table>
| Trade names | Meridia (US)  
Reductil (Europe) | Xenical             |
| Dosage   | 5–15 mg once daily                                                           | mg three times daily before meals |
| DEA schedule | Class IV                                                                  | Not scheduled       |
| Mechanism  | Reuptake inhibitor of serotonin and  
norepinephrine; promotes satiety;  
reducing food intake; mildly thermogenic | Pancreatic lipase inhibitor; blocks  
absorption of 30% of fat in intestine |
| Lifestyle requirement | Greatest efficacy is with structure  
meal plan that includes portion control | Diet should be consistent in 30% of  
energy content as fat; high fat  
indiscretions must be avoided |
| Cautions   | Blood pressure and pulse elevations may occur and  
patients should be monitored; should not be used  
with MAOIs; not recommended for use in  
patients with heart disease | Patients must be counseled regarding  
steatorrhea with high fat meals;  
vitamin supplement required |
What is Orlistat?

- **Trade name:** Xenical by Roche
- **Chemical name:** tetrahydrolipstatin
- **FDA approved in:** 1999
- **Dose:** 120 mg PO TID
- **Cost:** approx $139.00 each month

![Chemical structure of Orlistat]

\[\text{C}_{29}\text{H}_{55}\text{NO}_{5} = 495.74\]

\([2S-[2\alpha(R^\ast),3\beta]]-N\text{-formyl-L-leucine 1-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester}\]
How does Orlistat work?

- Inhibits fat digestion by blocking the enzymatic action of pancreatic lipase
- Dose-dependent inhibitor
- Decreases intestinal triglyceride hydrolysis
How does Orlistat work?

- Inactivates gastric and pancreatic lipase by forming a covalent bond with the serine residue site.
- This leaves triglycerides undigested, causing a steatorrheal diarrhea.
- Recommended to work best when given with a diet that has approximately 30% fat content.
What is a diet that is 30% fat?

- Patient 62 inches 110 lbs; BEE = 1200
- 30% kcal from fat would be 360 kcal
- 40 grams of fat each day

300 kcal 12 grams fat
126 kcal 2.7 grams
More examples of 40 grams of fat
Adverse reactions

Deficiency of fat-soluble vitamins can occur especially vitamin D. Recommended that patient take a multivitamin

Side effects: oily, spotty flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence (most commonly seen from a meta-analysis of nine clinical trials)

Weight loss (means ± SEM) during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients (LOCF data).

From: Torgerson: Diabetes Care, Volume 27(1).January 2004.155-161
In a review of 28 Randomized Clinical trials, it was shown to improve weight loss and improve serum lipid profiles. Total cholesterol, HDL, and LDL were improved.

XENDOS study

- Xenical in the prevention of diabetes in obese subjects
- 4 year double-blind randomized, placebo controlled prospective study carried out in 22 Swedish medical centers between 1997-2002
- 3,305 patients
- Lifestyle changes plus either orlistat 120 mg TID or placebo
XENDOS study

After 4 years, the cumulative incidence of diabetes was 9.0% placebo and 6.2% with orlistat (risk reduction 37.3% p=0.0032)

Mean weight loss was greater with orlistat (5.8 kg vs 3.0 kg with placebo) p<0.001

Note Orlistat is NOT Olestra

- Orlistat is a drug
- Olestra is a food additive
- Non absorbable fat substitute introduced in 1996
- Only approved for use in snack products by FDA
## Future in Obesity treatment

<table>
<thead>
<tr>
<th>Target</th>
<th>Delivery</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPY antagonist (Rimonanbant)</td>
<td>Intranasal (Pfizer)</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>Hypothalamus (PO Acomplia (Sanofi-Aventis)</td>
<td>Phase III</td>
<td></td>
</tr>
<tr>
<td>PYY</td>
<td>Intranasal (Merck)</td>
<td>Phase I</td>
</tr>
<tr>
<td>GLP-1</td>
<td>IV (Amylin)</td>
<td>Phase III</td>
</tr>
<tr>
<td>CCK</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Korner et al. Pharmacological Approaches to Weight Reduction 2004; JCEM 89(6):2616-2621
Summary

- Obesity increases GI diseases
- While most research has focused on its effects in the fields of cardiology and endocrinology, growing knowledge has been directed to the gut and its important role in contributing, managing, and eradicating obesity
- Growing research into using the gut as a target for treatment