Disclosures
I have the following relationships to disclose:

– Ethicon Endo Surgery Inc.
– Galectin Therapeutics
– Synageva Biopharma
– Raptor Pharmaceuticals

I will be discussing off-label use of medications in my presentation.

The Big Question:
What are the treatment options for NASH?
NASH Therapeutics

Lifestyle

Lifestyle

NASH Focused Clinic-Lifestyle advice

- Diet:
  - Increase fruits and vegetables
  - Eat healthy portion controlled breakfast
  - Decrease/avoid sugar sweetened beverages
  - Reduce take out/fast food meals

- Activity:
  - Increase physical activity
  - Reduce screen time

- Hepatotoxins
  - Alcohol in teens
  - Hepatitis A and B vaccination

What have we learned?
Is such a program effective?

Steatohepatitis Center: Outcomes

47% patients returned for 1 year follow-up

**Significant reduction in BMI, ALT and AST (*p<0.05).**


How rapidly can fibrotic NASH worsen?

<table>
<thead>
<tr>
<th></th>
<th>Baseline labs JAN 2009</th>
<th>Follow up labs APRIL 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>BMI</td>
<td>36.7</td>
<td>35.6</td>
</tr>
<tr>
<td>BMI %ile</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>110.2</td>
<td>118.7</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>ALT</td>
<td>161</td>
<td>191</td>
</tr>
<tr>
<td>AST</td>
<td>99</td>
<td>114</td>
</tr>
<tr>
<td>GGT</td>
<td>43</td>
<td>63</td>
</tr>
<tr>
<td>Hgb A1C (on metformin)</td>
<td>4.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>100</td>
<td>107</td>
</tr>
<tr>
<td>Psychotropic Meds</td>
<td>Abilify, lithium</td>
<td>No change</td>
</tr>
</tbody>
</table>

What if all this does not work?
Pediatric NASH with Stage 3 fibrosis

12 year old boy

Liver MR based Elastography

15 yo with NASH and mild/moderate diffuse fatty liver infiltration
Mean liver stiffness = 2.9 kPa (range 2.7-3.4)

ROC Curve for MRE in Children

- NAFLD patients (n=35)
- AUROC = 0.92 (0.79, 1.00)
- MRE able to identify significant fibrosis vs. no fibrosis (p=0.03)
  - 2.71 kPa
  - 88% sens
  - 85% spec

NASH Therapeutics

Lifestyle Rx/Sx Lifestyle

Agents studied well for treating NASH

- Insulin sensitizers
  - Metformin
  - Thiazolidinediones
- Anti-oxidants
  - Vitamin E
  - Cysteamine*
- Omega-3 fatty acids – no RCTs with histology

Landmark Randomized Placebo Controlled, Double Blinded Pediatric Trial for NAFLD with histologic outcomes
However, histological outcomes more promising for Vitamin E

- Compared to placebo, the % with histological NASH resolution at 96 week follow up biopsy:
  - 28% with placebo
  - 58% with vitamin E ($P = .006$)
  - 41% with metformin

Take Home Message: Vitamin E helps some, but not panacea for NASH

- Vitamin E reduces ballooning in NASH, and may lead to resolution of NASH in over ½ of pediatric patients with biopsy-proven NASH
- Both vitamin E and metformin no different from placebo in lowering ALT, AST levels after 2 years of therapy.

Cysteamine for the Treatment of NASH in Children (CyNCH)

- Cysteamine bitartrate – a cystine depleting agent

  \[
  H_2N\text{-}\text{SH} \quad \text{(Cysteamine)}
  \]

  - Increases intracellular glutathione and increases adiponectin multimerization
  - Pilot study of 11 children with NAFLD – significant improvement in ALT and AST after 24 weeks of treatment

NASH Therapeutics

Severe NASH now considered indication for surgery in adolescents

<table>
<thead>
<tr>
<th>Selection criteria for adolescent weight loss surgery</th>
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<tr>
<td><strong>BMI</strong></td>
</tr>
<tr>
<td>&gt; 35</td>
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<td>&gt; 40</td>
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Weight Loss Interventions

- Lifestyle
- Drug therapy
- Bariatric surgery

Pratt, JSA et al. Obesity 2009; 17:901
**Common Bariatric Surgery Procedures**

- Gastric Bypass
- Gastric Banding
- Sleeve Gastrectomy

**Bile Acid-FXR Pathway**


**FXR is a molecular target for the effects of vertical sleeve gastrectomy**


**Fxr ko mice can eat through a smaller stomach!**


So is that it?

Is FXR the answer?
**Not so fast ...**

**NASH Therapeutics**

- Lifestyle
- Rx/Sx
- Lifestyle

**What does the future hold?**

**Drugs in the Pipeline**

- Bile Acid Signaling/FXR: Obeticholic Acid
- Incretin/Insulin Sensitizers: Linagliptin, GW501516, GFT505
- Lipid Absorption/Metabolism: Ezetimibe, Orlistat
- Antioxidants/Anti-inflammatory: Resveratrol, Losartan
- Anti-fibrotic agents: Sintuzumab, Galectin (GA-MD-02)

**ClinicalTrials.gov**

- 81 studies recruiting!!
