Trends-in-Medicine

June 2006

by Lynne Peterson

SUMMARY

Sucampo/Takeda's lubiprostone has gotten off to a good start in chronic constipation, but the outlook is less certain in IBS-C, where Microbia's linaclotide is early but looks promising. Neither appears to be much of a challenge to Adolor/GlaxoSmithKline's alvimopan in opioid-induced constipation, but Progenics/Wyeth's methylnaltrexone could be, though it will first be subcutaneous. ♦ Use of biologic therapies for Crohn's Disease – and ulcerative colitis – is poised to increase, and doctors expect Abbott's Humira to capture the lion's share of the market, though most won't switch patients doing well on Johnson & Johnson's Remicade. UCB Pharma's Cimzia has the most convenient dosing (QM) but the least data, and it may have a harder time gaining traction. ♦ Salix's Xifaxan is approved for travelers' diarrhea but is getting widespread off-label use for all kinds of diarrhea. ♦ Doctors like the immediate-release pill formulation of Santaurus' Zegerid much better than the powder, and usage is likely to increase but not dramatically. ♦ Use of Allergan/Inamed's Lap-Band for obesity is likely to remain flat to increase slightly in the U.S. and decline slightly in Europe. ♦ There is a fair amount of interest in Shire's Mesavance for ulcerative colitis because reducing the pill burden is likely to increase compliance and, thus, response.

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

DIGESTIVE DISEASE WEEK (DDW)

Los Angeles, CA
May 20-25, 2006

DDW this year offered a look at a number of hot topics in gastrointestinal (GI) health, from new drugs for constipation to biologics for Crohn's Disease and agents to treat diarrhea, dyspepsia, gastroesophageal reflux disease (GERD), hepatitis C, ulcerative colitis, and pancreatic enzymes. There were also some new developments in endoscopy and a review of obesity surgery.

DDW is jointly sponsored by the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society for Surgery of the Alimentary Tract (SSAT). More than 16,000 people attended the meeting this year, and there were more than 4,000 posters.

CONSTIPATION

As many as 42 million Americans suffer from chronic constipation. Patients who suffer from chronic constipation often experience hard and/or lumpy stools, straining during defecation, a sensation of incomplete evacuation, and may have fewer than three bowel movements in a week. The discomfort of chronic constipation can greatly diminish a patient's quality of life as it impacts their ability to work and participate in normal daily activities.

Constipation is an almost universal side effect of opioid use, with up to 50% of cancer patients experiencing constipation. Adolor/GlaxoSmithKline's alvimopan is likely to be the next new drug for opioid-induced constipation (OIC). An expert commented, "Alvimopan is the most promising thing in opioid-induced constipation."

Many people with irritable bowel syndrome (IBS), a chronic condition marked by abdominal pain and disturbed bowel function, also suffer from constipation. One out of six adults in developed countries suffers from IBS, which accounts for 12% of adult visits to primary care physicians and is the most common disorder diagnosed by gastroenterologists. IBS affects millions of Americans and accounts for 25%-50% of referrals to gastroenterologists, but it is difficult to diagnose and treat effectively due to the variability of symptoms. Current therapies work in some patients but are limited in efficacy and have significant side effects. Of the three IBS subgroups – constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), and alternating or mixed (IBS-A or IBS-M) – 30%-40% of patients suffer from IBS-C, for which there currently are few available therapies.

At a Sucampo/Takeda-sponsored breakfast, the audience cited patient complaints related to constipation, but infrequency of bowel movements (BM) per week was cited by 37% of the doctors as the most common patient complaint.

Prevalence of Common Diseases

Measurement	Prevalence
Hypertension	21.6%
Constipation	15.5%
Migraines	15.1%
Diabetes	6.7%
Asthma	6.4%
Coronary heart disease	5.9%

Issues in Chronic Constipation

Question	Audience response	Data cited by speakers
What is the most common patient complaint?	Infrequency of bowel movements/week	81% straining 72% hard or lumpy stools 54% incomplete emptying 36% <3 BM/week
Does exercise improve constipation?	73% Yes	No, data indicate it is unclear that exercise improves bowel function among patients with constipation. It is unclear if an increase in physical activity affects GI motility or transit.
Does increasing dietary fiber improve constipation?	80% Yes	No, studies have shown limited improvement in both objective and subjective measures of constipation.
What percent of patients are satisfied with their current treatment?	66% said <50% of patients	47% of patients
What is the biggest challenge in treating chronic constipation?	32% lack of effective agent 30% improvement in some but not all symptoms 21% development of tolerance	Patients are concerned with overall quality of life, so efficacy, symptom improvement, tolerance, adverse events, and the limited number of agents are all a concern.

FDA-Approved and Investigational Drugs to Treat Constipation

Company	Drug	Type of agent	Method of action	Responders	Monthly cost *	Use	Issues
FDA approved drugs							
Generic	Lactulose	Osmotic agent	Enhances intestinal motility and secretion	N/A	$6.70 - $104.40	Short-term/ occasional treatment for constipation	Significant bloating limits use
Generic	PEG-3350 (polyethylene glycol)	Osmotic laxative	Increases osmolarity, luminal distensions, and peristalsis	69% at Week 1	$33.50	<2 week treatment of occasional constipation	May take week to work; long-term efficacy unclear
Novartis	Zelnorm (tegaserod)	5-HT_4-receptor agonist	Mimics serotonin and enhances peristaltic reflex	43% in Weeks 1-4	$161.40	Women with IBS-C; men and women <65 with chronic idiopathic constipation	---
Sucampo/Takeda	Amitiza (lubiprostone)	Chloride channel activator	Enhances intestinal fluid secretion	72% in Week 1	$145.80	Chronic idiopathic constipation in adults	Nausea 31.1%, Diarrhea 13.2%

Investigational agents			
Company	**Drug**	**Type of agent**	**Use**
Adolor/ GlaxoSmithKline	Alvimopan	Peripherally-acting μ-opioid receptor antagonist	Opioid-induced constipation
Microbia	Linaclotide (MD-1100)	Oral, QD, quanylate cyclase-C agonist	IBS-C, chronic constipation, and possibly opioid-induced constipation
Progenics/Wyeth	Methylnaltrexone	SC quaternary ammonium μ-opioid receptor antagonist	Opioid-induced constipation
Sucampo/Takeda	Amitiza (lubiprostone)	Chloride channel activator and enhances intestinal fluid secretion	IBS-C, opioid-induced constipation, and POI

* Wholesale

Source: Speakers at a Sucampo/Takeda-sponsored breakfast

Novartis's Zelnorm is approved for IBS-C, and doctors all use it, but they said there is still room for other new drugs. An expert said the number needed to treat for both IBS-C and IBS-mixed (IBS-M) is 7.

Asked how they would choose among the various agents, doctors offered these comments:

- "For chronic constipation, I really base it on cost and what is available, but I discuss the different methods of action. I base my decision on what the patient is willing to try, and then switch if that doesn't work…The order (in which we use new agents) may not matter; patients are always searching for something better."
- *Michigan:* "Cost does influence a lot of what we do as does formulary availability, especially with the elderly. It is unrealistic to say cost doesn't affect the decision…The simple reality is that, in the best case scenario, 50%-60% of patients improve with any drug, so there is a substantial percentage who don't respond to any particular drug."
- "Certainly there is a population that won't respond to anything available, so there is room for new agents…There are a lot of (IBS-C) patients who failed tegaserod, and that is where we would start."

Following is information presented on specific drugs in development.

ADOLOR/GLAXOSMITHKLINE'S alvimopan for gastro-intestinal recovery after small bowel resection

A pooled analysis was presented of patients from 3 randomized clinical trials.

Alvimopan Use For Small Bowel Resection

Measurement	Placebo n=50	Alvimopan 6 mg n=39	Alvimopan 12 mg n=65
Mean time to GI-3 recovery	109 hours	88 hours	73 hours
Mean time to GI-2 recovery	116 hours	92 hours	78 hours
Time to first bowel movement	94 hours	67 hours	66 hours

MICROBIA'S linaclotide (MD-1100) for IBS-C

The data are early, but the results of a 7-day Phase Ib safety, PK, and gastrointestinal PD study in healthy volunteers suggested linaclotide is a promising locally-active treatment of constipation-predominant irritable bowel syndrome (IBS-C) and chronic constipation (CC). A researcher said the company is also considering opioid-induced constipation trials.

Phase Ib Trial of Linaclotide in Healthy Volunteers
(statistically significant findings shaded in gray)

Measurement	Placebo n=16	3 µg linaclotide n=8	100 µg linaclotide n=8	300 µg linaclotide n=8	1000 µg linaclotide n=8
Headache	0	0	0	3 patients	1 patient
Flatulence	0	0	2 patients	1 patient	0
Constipation	2 patients	0	0	0	0
Patients withdrawing for adverse events	0	0	0	0	0
Stool consistency (rate 3-4 pre-treatment)	No significant change	No significant change	No significant change	Improved	Improved
Ease of stool passage (baseline score mostly 4)	No significant change	No significant change	No significant change	No significant change	Improved
Stool frequency	No significant change	No significant change	Improved but Nss	Improved but Nss	Improved but Nss
Mean time to bowel movement	No significant change	Decreased but Nss	Decreased but Nss	Decreased	Decreased
Stool weight	No significant change	No significant change	No significant change	No significant change	Increased

In the double-blind, placebo-controlled, multiple ascending dose study, linaclotide – an oral, QD, first-in-class oral guanylate cyclase-C (GC-C) agonist – showed no systemic exposure but improved a variety of markers related to intestinal transit, including stool consistency, stool weight, and time to first bowel movement.

At baseline, patients had an average of 3-7 bowel movements a week. No patients withdrew due to adverse events. A speaker said the lack of any statistically significant change in bowel movement frequency was due to healthy volunteers and the small size of the study. She predicted that with a larger patient population a more significant effect would be seen. The changes in stool consistency and ease of stool passage scores were small, but she said, "A significant number of people had a 1.5- or 2-point change, and what we've learned from talking with others in the field, is that a 2-point change would (be clinically relevant)."

Phase IIa studies in IBS-C and in chronic constipation are enrolling.

PROGENICS/WYETH'S methylnaltrexone (MNTX) for opioid-induced constipation and IBS-C

Data from a second Phase III trial found MNTX, a quaternary ammonium µ-opioid receptor antagonist administered subcutaneously every-other-day, is rapidly effective in reducing opioid-induced constipation. This trial was a two-week, double-blind, placebo-controlled, study of 133 patients with advanced illnesses who were in nursing homes, hospice, and palliative care centers. Eligible patients had a life expectancy of <6 months and <3 laxations in the prior week or no laxation in 48 hours. No rescue laxatives were allowed

within four hours of dosing. By Day 8, a blinded dose escalation was permitted (to MNTX 0.30 mg/kg or more placebo) if a patient did not have at least three bowel movements during the previous week that were not associated with rescue therapy. The most frequently reported adverse event was transient abdominal cramping.

A Progenics official said the company is assembling an NDA and plans to file MNTX with the FDA in early 2007. One of the reasons for the delay in filing is that the company is changing the formulation. The formulation tested in Phase III has to be refrigerated, but the company has developed a room temperature formulation, and that is the formulation that will be filed with the FDA. Before that can be filed, they need to complete a bioequivalence study in healthy volunteers and stability studies. An official said, "The new room temperature formulation will be easier for commercialization."

Progenics officials predicted MNTX will be used first by oncologists, geriatricians, palliative care doctors, and then hospice. A key advantage, according to Dr. Robert Israel, Senior Vice President for Medical Affairs at Progenics, is the quick onset of action, "Typically within minutes people feel some rumbling and GI relaxation. It works quickly. The median time to response is 15 minutes."

The biggest negative is the route of administration of the first formulation – subcutaneous injection. However, company officials presented this as a positive, not a negative. Dr. Israel said, "We had people on it for a year and a half, and they integrate it into their schedule, and they can plan for it. It is an injection, but because it is so predictable, they know they can have a bowel movement. Especially for people at the end of life or with respiratory compromise, it is a major undertaking to have a bowel movement, and they plan their day around it, so with methylnaltrexone they can plan it, and then go about their day…For us, that was the greatest unmet medical need."

Progenics plans to develop an IV and an oral form of MNTX. Dr. Israel said, "One of the distinguishing characteristics of this is the three dosing forms. We are filing for a subcutaneous formulation initially, but we have an IV and an oral formulation in development…We have blood levels established with all those. Subcutaneous is one injection, one laxation. The IV would be used in the post-operative setting where we want to maintain regular dose levels. In Phase II, we dosed the IV every six hours – the half-life is 6-9 hours – so there is a steady state in every stage of the recovery process, from clear liquids, first bowel movement, and discharge eligibility. Initially, with the oral we will be looking at reestablishing the Rome criterion, getting people up to 3 bowel movements per week. The subcutaneous is more for the acute setting or the nursing home or hospice setting, where getting patients to take an oral can be problematic."

Subcutaneous MNTX will compete with Adolor's oral drug, alvimopan, but Progenics and Wyeth officials believe the multiple formulations of MNTX will have advantages over alvimopan, including perhaps less nausea and decreasing urinary retention. Dr. Israel said, "Alvimopan is only oral, and it is available locally. It only works on the lumen of the GI tract, and if the GI tract is full, it will work its way down there slowly…Ours has a rapid onset and predictability in the most demanding setting…Alvimopan was never tested in the advanced illness setting, only post-op and now more what we call the chronic pain setting…Many people prefer a pill, but many also don't mind a shot…In the post-op setting, IV is preferred almost universally, and alvimopan can't be formulated as an IV. They have to pre-treat on an empty stomach (90 minutes to 2 hours prior to surgery), and we can be started in recovery. There are no regularly prescribed orals typically given after surgery. We have evidence that there may be additional benefits (to MNTX), such as a positive impact on urinary retention…We did a study in healthy volunteers, where we gave it by IV, and they had no feeling of a need to urinate, but given MNTX, many of them were able to urinate." A Wyeth official added, "Our drug doesn't cross the blood brain barrier, so there is no diminishing in pain control. It provides no pain relief itself, but it doesn't interfere with opioid pain control…MNTX also has a larger therapeutic window (than alvimopan)."

Asked if there is any issue with GI withdrawal, Dr. Israel said, "Alvimopan has had some problems with that. We have not seen it with SC or IV MNTX…I think that is because we are not concentrating in one area. We are hitting the whole gut via the circulatory system."

Results of Phase III MNTX-302 Trial of MNTX in Opioid-Induced Constipation

Measurement	MNTX 0.15 mg/kg SC every other day n=63	Placebo control (laxatives and stool softeners) n=71	p-value
Median time to laxation in responders	30 minutes	---	---
Primary endpoint #1: Laxation (bowel movement) within 4 hours of administration	48.4%	15.5%	<.0001
Primary endpoint #2: ≥2 laxations within 4 hours over first week (4 doses)	51.6%	8.5%	<.0001
≥1 laxations within 4 hours over first week (4 doses)	~70%	~30%	---
Patients who titrated up	~20 patients	---	---
Safety			
Serious adverse events	14 patients *	21 patients	---
Deaths	8 patients *	15 patients	---
Diarrhea	6.3%	4.2%	---
Peripheral edema	7.9%	11.3%	---
Body temperature increased	7.9%	2.8%	---
Dizziness	7.9%	2.8%	---
Nausea	11.1%	7%	---
Flatulence	12.7%	7%	---
Vomiting	12.7%	12.7%	---
Abdominal cramping	17.5%	12.7%	---

*** Not related or unlikely to be related to study drug**

SUCAMPO PHARMACEUTICALS/TAKEDA'S Amitiza (lubiprostone), approved for chronic constipation and in trials for IBS-C, opioid-induced constipation, and post-operative ileus (POI)

Amitiza was approved by the FDA in January 2006 and launched April 25, 2006. It is a novel type-2 chloride channel (ClC-2) activator, works by increasing fluid secretion, which helps improve function in the GI system. It has a pregnancy Class C rating, but the FDA requires a pregnancy test before use.

A Takeda official said Amitiza is in Phase II trials for opioid-induced constipation. There were no data on Amitiza in opioid-induced constipation at the American Pain Society meeting earlier in May 2006, and the official said the companies don't plan to talk about that indication until it is in Phase III. However, another official said there are no trials in opioid-induced constipation at this time. Asked what the advantages are of Amitiza over Novartis's Zelnorm, a source cited: utility in patients over age 65, the potential for combination therapy with Zelnorm, and another option for patients.

However, the outlook in IBS-C and ulcerative colitis is less certain. The company has decided to take a lower dose (16 µg) than that approved in chronic constipation (24 µg) forward into Phase III, and that trial is ongoing and either fully enrolled or nearly so. Data are expected at DDW 2007. The FDA also requested 12-month safety studies, and those are ongoing as well; the FDA reportedly would not accept the safety data from the chronic constipation trials for IBS-C.

A 12-week, dose-ranging, double-blind, placebo-controlled Phase II trial of Amitiza in IBS-C was presented at DDW, showing positive results and good tolerability in constipation-specific IBS patients. Adverse events and dropout rates generally increased with increasing dose. The FDA required hand x-rays in the trial, which a speaker said was due to concern about the properties of prostaglandins, which can have an effect on bone, but he insisted no bone issues were found.

Amitiza was prominently advertised at DDW, but few doctors questioned said they have started using it yet. Comments about Amitiza included:

- *Virginia:* "I was only detailed two weeks ago, and I haven't written a prescription yet because it is not available yet in my area."
- *Midwest:* "I wouldn't necessarily use it before Zelnorm. They have about the same efficacy. The issue with this – what makes it look promising – is that the preliminary news is that the nausea is manageable."
- "I'll use it in patients over age 65 and Zelnorm failures, depending on the cost and insurance coverage. I won't use it in combination with Zelnorm initially, but I will consider the combination in refractory patients."

Amitiza in IBS-C

Time period	Placebo	16 µg/day Amitiza	32 µg/day Amitiza	48 µg/day Amitiza
Abdominal pain (decrease from baseline)				
Month 1	0.19	0.45	0.40	0.46
Month 2	0.23	0.52	0.53	0.54
Month 3	0.34	0.56	0.59	0.53

Amitiza in IBS-C

Measurement	Efficacy (p<.05) vs. placebo		
	16 µg/day Amitiza	32 µg/day Amitiza	48 µg/day Amitiza
Improvement in constipation severity			
Month 1	Yes	Yes	Yes
Month 2	No	Yes	Yes
Month 3	No	Yes	Yes
Primary endpoint: **Improvement in abdominal discomfort/pain**			
Month 1	Yes	No	Yes
Month 2	Yes	Yes	Yes
Month 3	No	No	No
Improvement in bloating			
Month 1	Yes	No	Yes
Month 2	No	No	Yes
Month 3	No	No	No
Improvement in bowel movement frequency			
Month 1	No	Yes	Yes
Month 2	Yes	Yes	Yes
Month 3	No	Yes	Yes
Improvement in stool consistency			
Month 1	Yes	Yes	Yes
Month 2	No	No	Yes
Month 3	No	No	Yes
Improvement in straining			
Month 1	Yes	Yes	Yes
Month 2	Yes	Yes	Yes
Month 3	No	No	Yes
Safety			
Nausea *	19%	18%	31%

*** vs. 12% nausea with placebo**

- *Arizona:* "I use Amitiza in chronic constipation patients not responsive to Zelnorm, and I will use it in combination with Zelnorm. I start with 24 µg/day to see how much nausea there is…The mechanism of action is not fully delineated yet, but there is no change in electrolytes and no sign of dehydration. The nausea is pretty well handled by taking it with food…IBS patients have more bowel movements per week than chronic constipation patients, so maybe a lower dose will be enough in IBS."
- "I'm not sure we know the mechanism of action of this in IBS, and we do know the mechanism for Zelnorm…It hasn't been tested in ulcerative colitis, but there is a suggestion in animals that it might be effective in ischemic colitis."

Several posters reported in different studies with lubiprostone, including:

- **Morphine-induced constipation and analgesia.** The study found doses of 1 µg or higher significantly inhibited morphine-induced constipation but had no effect on the morphine analgesia, even at doses of 100 µg.
- **Gender differences in chronic constipation.** The study found both males and females had similar improvements in spontaneous bowel movements with 24 µg lubiprostone, but fewer male subjects experienced adverse events compared to females.
- **Long-term efficacy in chronic constipation.** A pooled analysis of three open-label, long-term (6-12 month) trials found significant improvements from baseline across all weeks for constipation severity, abdominal bloating, and abdominal discomfort.
- **Chronic constipation in elderly vs. non-elderly patients.** A pooled analysis of several clinical trials comparing elderly to non-elderly patients. The study found 24 µg BID was effective in both elderly and non-elderly patients, and elderly patients could tolerate the drug.

DIARRHEA

SALIX PHARMACEUTICALS' Xifaxan (rifaximin), a water soluble semi-synthetic antibiotic related to rifamycin that is FDA-approved to treat travelers' diarrhea. Doctors said they are using it widely off-label to treat other forms of diarrhea. In diarrhea-predominant IBS (IBS-D), a speaker said 400 mg TID is beneficial. A 10-day course of treatment provides benefits that appear to last about two months. He added, "The benefits extend to most component symptoms of IBS."

A study of 60 consecutive patients by Italian researchers found no difference in breath test normalization with rifaximin 1200 mg (60%) vs. rifaximin 1600 mg (63%). Dropouts were higher with the higher dose (0 vs. 2).

A study by UCLA researchers looked at the cost effectiveness of rifaximin in the management of hepatic encephalopathy. They reviewed ~11 studies of ~400 patients and concluded:

- It is not cost-effective as a first-line agent for either clinical or subclinical hepatic encephalopathy. If the cost were $1.03 per 200 mg tab, it would be cost-effective, the researchers found.

Cost-Effectiveness of Xifaxan in Hepatic Encephalopathy

Treatment	Cost per day	10-year cumulative cost of care	Life years gained
Do nothing	0	~ $68,500	~ 3.8
Neomycin	$3.61	~ $62,000	~ 5.2
Lactitol	$1.90	~ $60,000	~ 5.4
Lactulose	$1.90	$56,967	~ 5.7
Xifaxan	$21.84	$75,671	~ 6.3
Xifaxan salvage therapy	$21.84	~ $61,000	~ 6.8

- It may be highly cost-effective as a hybrid "salvage" therapy if reserved for patients failing lactulose, adding $1,894 to provide 1 added year of life.

An ongoing study in ciprofloxacin-resistant travelers' diarrhea is being conducted of U.S. military in Thailand, but it may be put on hold because travelers have not been getting diarrhea! An investigator said they need to wait until after the rainy season to start up again. The goal is a 20% reduction in diarrhea vs. placebo, but the results so far reportedly have been inconclusive, not negative. The primary endpoint is the number of cases of diarrhea (≥3 unformed stools and cramps in 24 hours). The trial is expected to enroll ~300 patients, with <75 enrolled so far.

Other comments on Xifaxan included:

- *Virginia:* "There are limited data, but I use it…There is a ton of off-label use, and off-label use is increasing because the toxicity is comparable to placebo. It seems to be working, and you don't have to expose patients to undue risk."
- *New York:* "It is easier to use and has fewer side effects than lactulose, which patients don't like because of the sweet taste. Rifaximin is very convenient, and it works very well. There is a 100% response rate."
- *Texas:* "I use a lot of rifaximin off-label for prophylaxis – to prevent travelers' diarrhea."

Off-label uses include: *Clostridium difficile (C. Diff)*, cryptic diarrhea – inflammatory bowel disease (IBD) and non-IBD – hepatic encephalopathy, IBS, pouchitis, diverticulitis, and colorectal surgery. Posters reported on the use of rifaximin in:

- **Refractory pouchitis.** A 13-patient, open-label, pilot study found that (1) rifaximin was safe and effective in improving symptoms in 81% of patients, and (2) it was effective maintenance therapy for a mean of 4 months. Six of the 13 patients who responded to rifaximin therapy were able to decrease or taper off other drug therapy. No adverse events were noted.
- **Hepatic encephalopathy.** The study found rifaximin was well tolerated, with a low incidence of adverse events, and it was effective in improving a variety of symptoms.

Xifaxan in Hepatic Encephalopathy

Symptom	Patients with symptom improvement n=37
Altered sleep patterns	67%
Slow/slurred speech	69%
Personality changes	75%
Reaction time	81%
Attention span	84%
Short-term memory loss	89%
Ability to perform mental tasks	89%
Asterixis	97%
Elevated serum ammonia	100%
Improvement in quality of life	100%

DYSPEPSIA

Depending on the definition used, from 19%-34% of people have dyspepsia. At one symposium, 41% of the audience estimated that 26%-50% of their patients have functional dyspepsia. The causes include structural disease – peptic ulcer, reflux esophagitis, cancer, celiac disease, and pancreatitis – but the vast majority are a functional disorder. The same audience said their major treatment for functional dyspepsia is a proton pump inhibitor (PPI), followed by a prokinetic or the combination of those two agents.

There is a lot of interest in new therapies for this, but the field is proving hard. Doctors haven't given up on Axcan's Itax (itopride), but they are waiting to see more details of the failed trial as well as the results of the ongoing trial.

Novel agents in development include:

Serotonin agonists/antagonists:

- **GLAXOSMITHKLINE'S Lotrenox (alosetron).**
- **NOVARTIS'S Zelnorm (tegaserod)** is in trials for dyspepsia. Phase II data suggest it may have some potential benefit, but it doesn't appear to significantly affect gastric emptying.
- **TAKEDA/DAINIPPON SUMOTOMO PHARMA'S mosapride.** This drug was described as "a bust."

Motilin agonists. Reportedly there is great interest in these agents.

- **ABBOTT'S ABT-229,** which failed in a 612-patient trial. In fact, in that trial ABT-229 was ***worse*** than placebo.
- **CHUGAI'S mitemcinal fumarate.** A poster reported on a post-hoc analysis that didn't look great, but the placebo response was high. Another poster reported on the results of a 12-week, 392-patient, double-blind, placebo-controlled, Phase IIb trial. The study found a significantly higher response rate in mitemcinal-treated patients. BMI and gender were independent covariates for a greater placebo response. Insulin-requiring diabetics with symptomatic gastroparesis who have a BMI <35 and HbA1c <10% may represent a subset of patients more likely to have a meaningful response with the higher dose (10 mg BID). No tachyphylaxis was observed during the 12-week study period.
- **GLAXOSMITHKLINE'S GSK-326416.** This small molecule that reportedly "kick starts natural motility" is in preclinical development. It isn't the agent going forward; the company has another unidentified agent which has just finished preclinical toxicology studies, and the company may soon enter clinical trials. A researcher said translational studies are also underway to identify a possible dose. A rabbit study was dosed IV, but an oral dose is being explored.

Acetylcholine auto-receptor inhibitors, such as **ASTELLA'S Z-338,** which is in Phase III for functional dyspepsia. In a 127-patient Phase II trial presented at DDW last year, the response rate was 75%-94%, compared to 65%-70% for placebo, but the difference was only statistically significant at one evaluated time point.

Dopamine-2 receptor inhibitors:

- **JOHNSON & JOHNSON'S Motilium (domperidone).** A speaker said, "I have patients clamoring for this drug, having read about it on the internet. How good is it? In 10 trials of a total of 273 patients there were impressive results, but these studies were generally miserable. My clinical impression is not very high. I've used it in practice, but I was never overwhelmed."
- **AXCAN'S Itax (itopride).** This is available in Japan. An international Phase III trial failed in January 2006 to meet its co-primary endpoints. A North American Phase III trial is underway. He said investigators in the first Phase III trial have not seen the data yet. Subanalyses are ongoing, and they only know the same top-line data as everyone else. An investigator said, "Right now the jury is out (on this)…I'm reserving judgment. We just don't know (how it will do) or when the data will be released." Asked about the utility in other indications if Itax fails in functional dyspepsia, he said, "It may help with constipation, GERD, or diabetic gastropathy." He said data should be ready from a nearly completed ongoing study on what Itax does to the stomach in terms of its method of action. Another investigator said it may have utility in IBS, "Gastroenterologists are desperate for remedies that work (in IBS), so we would love to find a subgroup in whom it works."

Other agents in Phase II development:

- **AGI THERAPEUTICS:**
  - AGI-001, a 5-HT1A receptor antagonist.
  - Oral arbaclofen (AGI-006).
- **DOR BIOPHARMA/LILLY'S** GTP-010.
- **GLAXOSMITHKLINE'S** vestipitant mesylate (GW-597599), an NK-1 antagonist.

ENDOSCOPY

Several studies presented at DDW reported on significant improvements in the quality and delivery of evaluation, diagnosis, and treatment of the GI tract and surrounding areas.

Transesophageal punctures of the heart. Researchers at Homerton University Hospital in London reported on the feasibility and safety of transesophageal punctures and interventions into the heart and coronary arteries in a pilot study in six pigs and two humans. Endoscopic ultrasound (EUS) is frequently performed with a scope to visualize and detect abnormalities in the GI tract, and the U.K. researchers found it is also useful to view coronary arteries and valves. They punctured the myocardium and aortic valve or coronary artery in the six pigs, three of which then received

angiography and three received thermal ablation of the aortic valve. Repeat puncture of the cardiac walls and injection of contrast to help visualize the tissues showed no complications, nor did the angiography or thermal ablation procedures. EUS-guided fine-needle aspiration of heart tissue for examination was done in the two humans, again with no arrhythmia or other complications.

A researcher said, "Our studies suggest that using a trans-esophageal process to gain access to the heart may be feasible and safe for patients as an alternative to the much longer, indirect route through the femoral artery in the groin or to open surgery. This may be of specific interest for patients who have damaged heart muscle after a heart attack and may benefit from the injection of therapies directly into the muscle without another operation." They suggested this may be especially useful for the injection of growth factor in the heart after an myocardial infarction (MI).

A role for both Double Balloon Enteroscopy (DBE) and Capsule Endoscopy (CE). A multicenter U.S. case review study looking at the accuracy of these two procedures found that they both offer value to patients with unknown sources of intestinal bleeding or other small bowel problems, and both can be used to help evaluate a patient's health. The lead researcher, Dr. Shahab Mehdizadeh of Cedars-Sinai Medical Center said, "Clearly, DBE has the advantage of being able to treat problems. But we believe that…CE should continue to be used as a valuable regular screening test for bowel abnormalities, while DBE will be a better procedure for conformation and treatment of small-bowel problems."

During a capsule endoscopy, the patient swallows a small camera that records images of the intestinal tract. In a DBE, doctors use a scope fitted with two balloons to navigate the entire small bowel. When inflated with air, the balloons can expand sections of the small intestine to allow the camera a closer examination.

DBE was conducted in 130 patients. Of these patients, 115 had previously undergone CE, which had found potential bleeding sites in 63 of those patients and negative results in the other 52 patients. The DBE results showed a bleeding site in two-thirds (41 patients) of the patients who had the same reading by CE, and one-third (16 patients) in the group with clean CE. DBE was also able to treat nearly all the bleeding sites found.

Overall, the two procedures were considered moderately effective in detecting sources of intestinal bleeding. Efficacy rates for DBE and CE were comparable in detecting ulcers, blood vessel abnormalities that cause bleeding, and large masses; but DBE was more effective in detecting mucosal and submucosal polyps.

Comparison of CE and DBE

Measurement	Capsule endoscopy n=115	Double balloon enteroscopy of the CE patients
Potential bleeding sites detected	63 positive (54.8%) 52 negative (45.2%)	41 of the CE positive (65.1%) 16 of the CE negative (30.1%)
Miss rate	20.3%	27.8%
Duration of exam	44 minutes	94 minutes
Ulcer identification	Substantially the same (p<.0001)	
Large mass identification	Moderate agreement (p<.0001)	
Identification of mucosal/submucosal polyps	Disagreement, perhaps due to false positives on CE	
Advantages	Faster, less uncomfortable for the patient	More effective in detecting mucosal and submucosal polyps
Disadvantages	Missed some abnormalities	Did not read entire small bowel in single procedure
Best use	Screening	Confirmatory/therapeutic

Endoscopic ultrasound of the vascular system. Johns Hopkins researchers tested the feasibility of using EUS to perform vascular angiography in three pigs to identify major blood vessels. During the EUS, the researchers injected contrast to improve vascular visualization, and performed angiography using several different gauge aspirate needles (19g, 22g, and 25g). The process demonstrated excellent visualization of the vasculature, without any technical difficulties in injecting each artery.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Speakers at a Santaurus-sponsored symposium pointed out a problem with all delayed-release proton pump inhibitors (DR-PPIs) – nocturnal breakthrough that can disrupt a patient's sleep. Morning dosing of DR-PPIs inhibits daytime acid secretion, but some recovery of basal overnight intragastric acidity is seen with all DR-PPIs. The American College of Gastroenterology practice guidelines recommend giving DR-PPIs before food.

The FDA has not approved BID dosing of DR-PPIs, but the addition of an H2-receptor antagonist (H2RA) – e.g., ranitidine – at bedtime can help some patients. As a result, new PPIs continue to be introduced and investigated. Santaurus has developed an immediate-release PPI (IR-PPI), and Negma-Gild is working on a true once-a-day PPI, tenatoprazole.

NEGMA-GILD'S tenatoprazole

This novel proton pump inhibitor has a 7-hour plasma half-life and early trials indicate it may be more effective than AstraZeneca's Nexium (esomeprazole). A Negma-Gild official said the company expects to start Phase III trials soon and hopes to bring it to the U.S. market by 2009. They also plan to study an every-other day dosing. He said, tenatoprazole is as effective as 18 mg Nexium BID, but at three days post-treatment, tenatoprazole was superior to Nexium. While DR-PPIs are generally given in the morning, the optimum time to

administer tenatoprazole appears to be 7 pm. The official said there is a positive effect on sleep "even the first night" with tenatoprazole. An expert said, "It has very prolonged inhibition vs. other PPIs. Others reach optimal inhibition in about three days, and this reaches it in two days."

A poster reported on tenatoprazole in 12 healthy male subjects. It found 7-day administration of 40 mg tenatoprazole QD controlled intragastric acidity throughout the night, with little effect on food intake and time of dosing.

SANTAURUS' Zegerid

This immediate-release combination of the PPI omeprazole and an antacid, sodium bicarbonate, first came out as a powder, but doctors reported that patients didn't like that formulation. Now, the company has introduced a capsule, and doctors said it is an improvement over the powder. Many said they have tried it, mostly replacing the powder with the pills, and it is likely usage will increase, but not dramatically. A Rhode Island doctor said, "I used it once, but the (generic DR) PPIs are cheaper. I'm not sure any of them (brand PPIs) are worth an extra $3/day." A New York doctor said, "I just started using it. Nocturnal acid breakthrough (NAB) is real, and this makes sense and works." A Michigan doctor said, "The problem is insurance." Another doctor said, "Patients get referred to me when the primary care doctor tried a DR-PPI, and it failed to relieve nocturnal heartburn. If pH is normal, I consider (Zegerid)…Patients don't get reflux when they are sleeping, but they do when they are lying down." A Midwest doctor predicted Santaurus has an "uphill battle" ahead in marketing Zegerid because of generics, formularies, insurance, and Nexium's name recognition, "Without being on formularies, it is very difficult to penetrate the market."

HEPATITIS C (HCV)

Most of the HCV data at DDW was a repeat of information already presented at the European Association for the Study of the Liver (EASL) in Vienna, Austria, in late April 2006. However, there were a few new items of interest.

COLEY PHARMACEUTICAL GROUP'S Actilon (CPG-10101), a TLR-9

Incremental new data on Actilon were presented on a Phase Ib trial first presented at EASL in April 2006. The trial was a 74-patient, five-arm study of subcutaneous injection of 0.2 mg/kg QW Actilon alone and in combination with peg-IFN + RBV in treatment-refractory HCV patients. Patients who achieved >2 log reduction in HCV RNA were eligible to continue on Actilon therapy for a total of 48 weeks and will be followed for an additional 24 weeks to monitor for SVR. At DDW, researchers reported on continuation therapy at Weeks 12 and 24. They found that HCV RNA undetectable responses have been maintained out to 32 weeks of treatment in the Actilon + peg-IFN + RBV arm thus far, with no evidence of breakthrough.

INTERMUNE'S ITMN-191 (formerly ITMN-B)

The company said it plans to submit this inhibitor of NS3/4A protease to European regulators in 3Q06. A speaker said it is liver trough levels that are thought to be important for the emergence of resistance. A speaker said that ITMN-191, unlike Boehringer Ingelheim's discontinued BILN-2061, retains significant potency against the D168V mutation. He also said ITMN-191 has a "favorable" cross-resistance profile with Vertex's VX-950. Another source said the company is hopeful that it will be able to do BID dosing and expects to have ITMN-191 in the clinic in the fall in Europe. He said, "This is already as 'boosted' as VX-950 and SCH-503034 would be with (Abbott's) ritonavir."

VERTEX'S VX-950, a protease inhibitor

Data were presented on 28-day triplet therapy of 750 mg VX-950, an oral protease inhibitor for HCV, in combination with 180 µg peg-IFN-α-2a weekly and either 1000 or 1200 mg RBV daily. After 28 days, patients began standard therapy with peg-IFN/RBV for 12 weeks. Researchers reported the combination is well-tolerated and effective, appearing to prevent clinical breakthrough and to suppress the emergence of NS3 protease inhibitor-resistant variants. Adverse events were similar to those observed in previous studies of pegylated interferon and ribavirin, and no serious adverse events were observed. The most common adverse events were mild-to-moderate flu-like illness, fatigue, headache, nausea, anemia, depression, itching, and rash.

Despite the detection of treatment-emergent viral variants in two patients early in the course of VX-950 dosing, combination treatment with VX-950 resulted in a continuous decline in HCV RNA to undetectable levels through the initial 28-day dosing period, and HCV RNA has remained undetectable in these patients through 12 weeks of follow-on therapy. At 28-days, all 12 patients had undetectable HCV RNA, and at 12 weeks post-triple therapy, 11 patients (92%) had no detectable virus in their blood. The 12th patient was found to have detectable HCV RNA (less than 30 IU/mL) in

Preliminary Data on Actilon Continuation Therapy in Patients with Early Viral Response (EVR)

Measurement	Peg-IFN + RBV n=15	Actilon + peg-IFN + RBV n=14	Actilon + peg-IFN n=16	Actilon + RBV n=15	Actilon n=14
HCV RNA undetectable at Week 24	N/A	6 patients	3 patients	0	N/A
HCV RNA undetectable any time during first 12 weeks or in continuation	N/A	9 patients	5 patients	0	N/A
HCV RNA mean log reduction at Week 24	N/A	3.61	2.99	(0.33)	N/A

the Week 12 post-VX-950 follow-up sample, with continuing evidence of detectable HCV RNA in subsequent samples. All 12 patients are continuing to receive peg-IFN + RBV.

The question is what happened with the 12th patient. A Vertex official said, "Four weeks (of triplet therapy) is probably not enough, but the experts we've asked think 11 of 12 patients is very good…Patient No. 12 may have been a true non-responder (to peg-IFN + RBV). In that patient HCV RNA was detectable at Week 2, then undetectable, and then detectable again at Week 12…We don't think this is a non-compliant patient. Body mass index (BMI), which is an independent predictor of non-response to interferon, may have something to do with it. We are continuing to treat the patient with peg-IFN + RBV, and HCV RNA is 490."

HCV RNA Suppression with VX-950 + Peg-IFN/RBV

Time period	HCV RNA >30 IU/mL	HCV RNA <30 IU/mL (below limit of quantitation)	HCV RNA <10 IU/mL (undetectable)
Day 8	6	6	2
Day 15	1	11	3
Day 22	0	12	9
Day 28	0	12	12

Results of the VX-05-950-102 Study of VX-950 + Pegasys + Copegus

Measurement	750 mg VX-950 q8h n=12
Undetectable HCV RNA at 8 days	2 patients
Undetectable HCV RNA at 28 days	All 12 patients (100%)
Undetectable HCV RNA at Week 16	11 patients (92%) *
Viral breakthrough	0
Serious adverse events	0
Treatment discontinuations	0

* 12th patient had HCV RNA <30 IU/mL

WYETH'S HCV-796. At EASL, a randomized 14-day Phase Ib ascending, single-dose trial was presented, indicating this agent is well tolerated. Data at DDW from a multiple ascending dose study indicate it also is effective. In that study, reseachers reported they saw activity in non-genotype-1 patients. One researcher said, "We could have gone to higher doses, but with maximum exposure at 1000 mg, we saw no reason to go further…Peak response was with the 500-1000 mg Q12 doses."

The most common or important side effects were mild-to-moderate headache and a slight increase in bilirubin across all doses. The researcher said, "On average the bilirubin increase was <0.5, but it was real, and it happened at every dose. We will be watching that closely." There also was a decrease at all doses in ALT.

Asked if Wyeth is pursing combination therapy, the researcher said, "Our first step is obviously combining it with IFN… We have set the stage to work with other small companies because we realize that is the future."

Asked if there was any evidence of hemolysis, he said, "We did quite a bit of preclinical work on resistance…We will present that in great detail probably at the liver (AASLD) meeting later this year."

INFLAMMATORY BOWEL DISEASE (IBD)

IBD can involve either the small or the large bowel, or both. Crohn's disease and ulcerative colitis (UC) are the best known forms of IBD.

Crohn's Disease

Biologic therapies to treat Crohn's disease got a lot of attention at DDW. Experts predicted their use will increase and described all of them as comparable in efficacy. There are about 600,000 to a million Crohn's patients in the U.S.

Currently, only Johnson & Johnson's Remicade (infliximab) has FDA approval, but Abbott's Humira (adalimumab), which is approved in rheumatoid arthritis, is expected to get approval in Crohn's in 2007, and some doctors are already using it off-label, primarily for patients who fail Remicade. UCB Pharma's Cimzia (certolizumab) is in Phase III development.

The FDA has decided to allow Biogen Idec/Elan's Tysabri (natalizumab) to return to the market as a treatment for multiple sclerosis, and off-label use in Crohn's disease is possible, but may be difficult, given the strict distribution system and risk management program (RiskMAP) required. It was expected that it would take about three months for Tysabri to be launched after the FDA issued its decision, but Biogen Idec and Elan officials now expect to be able to launch it in July 2006. At DDW, Elan officials also indicated that no new trials were expected to be required in Crohn's, and they said they planned to file for an indication for Tysabri in Crohn's based on the already completed trials, but that decision hinged on the final terms of the RiskMAP, and so it is not clear whether the final RiskMAP will cause the companies to change their mind about the Tysabri strategy in Crohn's.

How will doctors choose among the biologics? Generally, doctors said they would not switch patients doing well on Remicade, but they would consider other agents for non-responders, for patients who lose effect after a boost in Remicade dosage (up to a maximum of 10 mg/kg), and for new patients. Currently, doctors questioned said use of biologics would increase from an average of 21% of their Crohn's patients today (on Remicade) to 25% of their patients in 6-12 months (on all biologics together). The breakdown of the predicted use of the different agents is detailed in the chart on the next page (*Page 11*).

Estimates of Biologic Use in Crohn's Disease

Drug	Use in 6-12 months
Remicade	13%
Humira	8%
Cimzia	4%
Tysabri	1%

Among the comments on the TNF inhibitors were:

- "This is the theme of this entire DDW…The way I will handle it is to sit patients down, inform them (of their options), see what they are willing to risk. In my mind, they (the biologics) are all fairly close in induction therapeutics. I will discuss which might be the best for them."
- "I don't think there is any difference among the three anti-TNFs. The infliximab and adalimumab data look pretty similar. I conclude they all have broadly similar efficacy in maintenance of remission at Week 26-30 in active Crohn's. Only clinical trials with infliximab and adalimumab have demonstrated maintenance of remission out to 1 year…Caution should be exercised when comparing clinical trial results because of variations in patient selection."
- "I think we will make the choice together (patient and doctor). Most patients will prefer the convenience of subcutaneous injection. Most patients are not disabled, and those who are still working will not want to come in for an infusion (with Remicade), but some will want to stay with infusions."
- "There are pros and cons to each…I expect to talk about each agent, and if I feel strongly, I'll say so to the patient, but I think most of the time patients will have a lot of say about it – and so will the insurance companies."
- *Rhode Island:* "I'll continue to use only Remicade. I won't use the others quickly. Insurance coverage is good for Remicade."
- *Missouri:* "I don't use any Humira off-label now. When all three TNF inhibitors are available, use of administration will dictate use."
- *Virginia #1:* "First-to-market gives Remicade durability. The appeal for some doctors is that they know they get compliance when they use Remicade, and the patients are in the office for the lab tests, so they don't have to refuse a refill because the patients haven't had their lab tests. Humira will take off like crazy. The dosing chapter is not closed. People will use higher doses of Remicade, and then convenience and cost will be a factor. Cimzia may have a different (better) safety profile. All anti-TNFs are not the same."
- *Canada:* "If a patient fails one TNF, the response rate will be low with another."
- *Virginia #2:* "I will switch my Remicade patients to Humira. Once I see Humira is effective, I won't use Remicade again, but I don't plan to use any Cimzia or Tysabri."
- *New York:* "Infliximab taught us not to settle for less, not to let patients fester with symptoms or lose their bowel. But TNF inhibitors don't work in everyone; about 60% respond well, looking and feeling better – well enough for them. For 30%-40% the response is not dramatic… Tysabri is amazing, and I know it works in non-TNF responders, but can we identify people at risk (of PML)? So (NPS Pharmaceuticals') teduglutide will be great; it's a completely different approach, and the rate of remission is high. Teduglutide may fill a void for TNF inhibitor non-responders. And over time, TNF inhibitor responders lose the effect. There is a decay of effect over time, which could be due to immunogenicity…The two other TNF inhibitors look good. Humira doesn't show much decay or dose escalation over a year…Route of administration will be an issue. Some patients like infusions, and some don't. It will be nice to give patients a choice…If I had a naïve Crohn's patient, I'd pick Cimzia or Humira. The immunogenicity is very low with Humira, and the durability showed good data, but Humira is more expensive than Remicade…The Cimzia data were lacking. My beef with the study was that non-responders who dropped out could go to the open-label trial. The results look modest, but my gestalt is that it works. The numbers look kind of pokey."
- *Rhode Island:* "About 10% of my Crohn's patients are on Remicade, and I don't think that will expand much over six months. Humira would be No. 2 because the administration is a big benefit. I would absolutely not switch patients off Remicade, but I might consider Humira for new patients – though I'll probably stick with Remicade. Tertiary centers will use more biologics than community doctors. The tough patients we will refer on…I had one ulcerative colitis patient for whom I tried Remicade. As a last salvage, I would try a biologic in UC patients."

Asked how close we are to a perfect anti-TNF agent, Dr. William Sandborn of the Mayo Clinic said, "I think we will see at least one more anti-TNF developed for IBD…Are there any differences in safety? My sense is that we will see rare events with all the agents…There probably can be variations in injection site reactions and immunogenicity. You also have to think of speed of onset and dosing – IV vs. SC…I'm not sure we will see a lot of advances."

Asked if there is a clinically relevant difference in the speed of onset of action of the various agents, an expert said, "It is difficult to tell…(With infliximab), it looks like the maximum effect is not later than Week 6. With certolizumab, you see efficacy climb over Weeks 0-2-4, and then in some patients there is an additional climb thereafter. That is also true with adalimumab, with patients remitting as late as Week 12. The

Anti-TNF Therapies for Crohn's Disease

Therapy	Advantages	Disadvantages
Aminosalicylates	Oral	Stevens-Johnson Syndrome
Antibiotics: metronidazole	Uncontrolled studies suggest use for perianal Crohn's disease	Conflicting efficacy data
Ciprofloxacin	N/A	Efficacy data underwhelming
Enteric release corticosteroids: budesonide	Wealth of data to show effective in induction and modest data on maintenance, less likely to cause steroid-induced side effects	Long-term steroid use causes a multitude of problems
Azathioprine	Improves remission rates and decreases steroid requirements	Leukopenia
Methotrexate	Improves remission rate and decreases steroid requirements; may be effective in patients refractory to 6-MP	Contraindicated in pregnancy, rare hypersensitivity pneumonitis

Top-Down vs. Step-Up Therapy

Order	Top-down	Step-Up
Initial treatment	TNF inhibitor + azathioprine	Budesonide, antibiotics, 5-ASA
Next steps	Episodic TNF inhibitor	Methotrexate
		TNF inhibitor
Final treatment	Steroids	Surgery
Efficacy		
Remission off steroids at 6 months	75%	48%
Remission off steroids at 12 months	77%	64%
Use of azathioprine at 12 months	94%	63%

Characteristics of Drugs Used for Crohn's Disease

Measurement	5-ASAs	Antibiotics	Budesonide	Conventional steroids	6-MP/AZA MTX	Anti-TNF biologics
Short-term response	–	±	+	+	–	+
Long-term remission	–	±	±	–	+	+
Mucosal healing	–	?	–	–	+	+
Safety	+	+	+	–	+	+
Altered natural history	–	?	Unlikely	–	Possibly	Possibly

Biologics in the Treatment of Crohn's Disease

Biologic therapy	Characteristics	Dosing	Advantages	Disadvantages
Abbott's Humira (adalimumab)	Human recombinant antibody	SC Q2W	Effective in many patients with loss of response or intolerance to Remicade	Antibody formation
Biogen Idec/Elan's Tysabri (natalizumab)	Anti-alpha-4 integrin monoclonal antibody	Infusion	Efficacy as good or better than TNF inhibitors	Rare cases of PML
Johnson & Johnson's Remicade (infliximab)	Chimeric monoclonal antibody	Infusion	Oldest, most studied, effective at inducing remission and maintaining it	Immunogenicity, infusion reactions, infections, lymphoma, etc.
Johnson & Johnson/ Schering-Plough's golimumab (CNTO-148)	Fully human monoclonal antibody	SC	N/A	N/A
Millennium Pharmaceuticals/ Genentech's MLN-02	Anti-alpha4beta7	N/A	There does appear to be a drug effect.	Pilot studies didn't show a benefit.
PDL BioPharma/Biogen Idec's HuZAF (fontolizumab)	Anti-IFN-γ (anti-IL-12)	IV (Oral?)	Development currently focused on rheumatoid arthritis	
PDL BioPharma's Nuvion (visilizumab)	Anti-CD3 monoclonal antibody	IV	Might improve disease without causing immune suppression	N/A
Roche/Chugai's Actemra (tocilizumab)	Humanized anti-human IL-6 receptor monoclonal antibody	SC QW	N/A	N/A
Schering AG/Berlex's sargramostim	rhuGM-CSF	Daily SC for 8 weeks	May improve quality of life. There appears to be drug activity.	Difficult to take: bone pain, injection site reactions. Missed the primary endpoint in a trial.
UCB Pharma's Cimzia (certolizumab pegol)	Pegylated humanized antibody Fab' fragment against TNF	SC Q4W	PRECiSE-2 trial showed significant improvement over placebo in clinical response (26.6%) and clinical remission (19.3%) at Week 26.	Phase II open-label trial showed no benefit over placebo on clinical response.

maximal effect with all three is within six weeks, and there is additional benefit out to three months with certolizumab and adalimumab that you don't see beyond Week 6 with infliximab." Another expert said, "If a patient doesn't respond in six weeks, it is unlikely the patient will respond." A third expert said, "We are used to the infliximab 'high' patients get. With another agent, it is a little more gradual. One patient described no longer having the 'roller coaster effect' when switched from infliximab to adalimumab. He felt well again."

Asked if the agents can be used consecutively, an expert said, "I haven't completely worked this out…If a patient had, say, a nice response to Remicade, but now, instead of it lasting 8 weeks, it lasts 7 weeks. Will I switch that patient? No. At six weeks? Probably not. At five weeks? Probably…10 mg/kg of Remicade doubles the cost. Would I really double the cost? That is an enormous increase in cost, but if a patient did really well (on Remicade) and you know you could recapture many of those patients with a dose doubling, that makes it a little uncertain. When you look at the rheumatology literature, it is pretty awful, so we have to work it out ourselves…I kind of think I will dose escalate with a drug that is working before I switch, but I need to work that out."

How big a role does reimbursement play? Doctors generally indicated that it is very important since the biologics are very expensive. However, they pointed out that coverage has been very good for Remicade, and they anticipate the other TNF inhibitors will also be covered. Usage of new TNF inhibitors will be minimal, they predicted, until and unless they are covered by insurance. A doctor said, "Remicade is well-covered with a low or no co-pay, even for patients with normally high co-pays."

Numerous lectures included a discussion of top-down vs. step-up treatment. Experts pointed out that top-down has shown interesting benefits and predicted that top-down will be adopted – in the future. For now, most experts as well as community doctors continue to use a step-up approach, starting with antibiotics or 5-ASA and working their way up to biologics and, finally, surgery when patients don't respond or worsen. A doctor said, "Right now, I do step-up, but as the data reach the public and get dissected and discussed, then top-down will increase."

However, the best options still only reduce relapse by ~50%, a speaker noted, citing several advantages to the biologics:

- Different mechanisms of action.
- Similar rates of clinical remission.
- New approaches for moderate-to-severe Crohn's.
- Rational combination therapy.
- Possibly less immunogenicity.
- Possibly less risk of infection.
- Improved quality of life.

56-Week CHARM Trial Results

Measurement	Humira 40 mg EOW n=170	Humira 40 mg QW n=172	Placebo n=157
Primary endpoint #1: CDAI<150 (remission) at Week 26	40%	46%	17%
Primary endpoint #2: CDAI<150 (remission) at Week 56	36%	41%	12%
CDAI decrease ≥100 points from baseline at Week 26	52%	52%	26%
CDAI decrease ≥100 points from baseline at Week 56	41%	48%	16%
CDAI decrease ≥70 points from baseline at Week 26	54%	56%	28%
CDAI decrease ≥70 points from baseline at Week 56	43%	49%	18%
Steroid-free remission (CDAI<150) at Week 26	35% (p<.001)	30% (p<.001)	3%
Steroid-free remission (CDAI<150) at Week 56	29% (p<.008)	23% (p<.008)	6%
Complete fistula closure at last 2 visits	36%	46%	14%

ABBOTT'S Humira (adalimumab)

The CHARM trial found Humira induces and maintains clinical response and remission in Crohn's patients. CHARM was a 56-week, randomized, double-blind, placebo-controlled, multicenter study in 854 moderate-to-severe Crohn's patients – Crohn's Disease Activity Index (CDAI) of 220-450. Patients first underwent a 2-week induction period, receiving 80 mg at Week 0 and 40 mg at Week 2. The 499 patients (58%) who achieved clinical response (CDAI≥70) were then randomized to one of two doses of Humira vs. placebo.

BIOGEN IDEC/ELAN'S Tysabri (natalizumab)

Tysabri was in clinical trials for both Crohn's and multiple sclerosis (MS) when it was pulled from the market in February 2005 after three patients developed PML (progressive multifocal leukoencephalopathy). In March 2006 an FDA panel recommended Tysabri be allowed to come back on the market – with a risk management plan (RiskMAP) – and the FDA on June 5, 2006, announced that Tysabri can come back on the market – with a tough risk management plan and severe restrictions: a black box and a restricted distribution system. The companies said they hope to re-launch the drug in July.

The FDA said:

- Tysabri should be used only as monotherapy.
- Patients ***should*** only get Tysabri if they have failed another MS therapy, but that is not a requirement.
- Doctors, infusion centers, and pharmacies must register with the companies' TOUCH program before prescribing Tysabri. And only registered doctors can prescribe it.
- Patients must enroll/register to receive Tysabri.

- Patients must have an MRI before getting Tysabri and must be evaluated at three months, six months, and every six months therafter, with those evaluations reported to Biogen Idec.

Tysabri got a relatively warm reception at DDW, with experts emphasizing its efficacy but also warning of the risk of PML. Doctors who were asked about the outlook for Tysabri said they doubted there would be much off-label use in Crohn's for three reasons: (1) The FDA RiskMAP may not permit it, (2) Payors may not cover it, and (3) They would be reluctant to prescribe it. Doctors at academic centers generally indicated they might use Tysabri off-label for the most refractory patients, but most community doctors said they would wait for FDA approval. An expert said, "I think it is approvable for Crohn's. If it comes back for MS, then the question is whether there are patients you would treat with it, and 30% of the audience at a session yesterday said there are patients, refractory patients, not early disease."

Results of ENCORE Tysabri Trial in Crohn's

Measurement	Placebo n=250	Tysabri n=259	p-value
Mean age	38.1	37.7	---
Response after first infusion	37%	51%	---
Response at Week 4	40%	56%	---
Response at Week 8	44%	60%	---
Primary endpoint #1: CDAI decrease ≥70 points from baseline by Week 8 that was sustained through Week 12	32%	48%	<.001
CDAI decrease ≥70 points from baseline at Weeks 8 and 12	22.5%	32.0%	---
Remission (CDAI<150) at Weeks 8 and 12	16%	26%	0.002
Response in patients with CDAI>330			
Response at Week 4	39%	57%	---
Response at Week 8	37%	62%	---
Response at Week 12	37%	60%	---
Response at Weeks 8 and 12	27%	51%	---
Response at Weeks 8 and 12 based on CRP			
CRP 2.87 mg/L	32%	49%	<.001
CRP 5 mg/L	32%	51%	---
CRP 25 mg/L	11%	33%	.003
CRP 50 mg/L	8%	33%	0.051
CRP 100 mg/L	15%	31%	.001
Safety			
Adverse events	82%	85%	---
Serious adverse events	10%	N/A	---
Headache	21%	29%	<.05
Nausea	12%	15%	---
Nasopharyngitis	6%	11%	---
Flare of Crohn's disease	N/A	Greater	---
Infections and infestations	30%	35%	---
Serious infections	2%	<1%	---
Antibody formation	---	9.5%	---
Results in patients with antibodies			
Adverse events	---	87% in AB+ 86% in AB-	---
Response	---	39% in AB+ 50% in AB-	Nss

Results of Tysabri Safety Review

Measurement	Tysabri n=259
Enrollment	91% of Crohn's patients 87% of MS patients 92% of RA patients
Patients with CSF analyzed for JC virus	6% Crohn's 16% MS 4% RA
Patients with plasma analyzed for JC virus	88% of Crohn's 56% of MS 95% of RA
Additional cases of PML	0

The results of the Tysabri PML (safety review in >3,500 Crohn's, MS, and RA patients treated with Tysabri in clinical trials) were presented which, as has already been reported, found no additional cases of PML. An investigator said, "The risk is 1:1000 in MS, and the risk of 1:1000 in Crohn's. Together, the risk is 1:1000."

Efficacy results were presented from the 8-week, international, randomized, double-blind, placebo-controlled, Phase III ENCORE trial of Tysabri in moderate-to-severe Crohn's patients with CRP levels >2.87 mg/L. The trial found Tysabri induced a response by Week 8, and that response was maintained to Week 12. Researchers concluded that the response and remission rates confirmed the efficacy of natalizumab as induction therapy.

A poster by Dr. Bruce Sands of Harvard and colleagues, sponsored by Elan and Biogen Idec, reported on a survey of 61 patients about their willingness to accept the risks of serious adverse events in exchange for clinical benefits. Not surprisingly, the study found the maximum acceptable risk of death or disability from PML for a clinically relevant benefit level is well above an extrapolation of the currently observed rate of this adverse event. About 90% of patients said they would accept the currently estimated risk of PML death or disability to obtain a clinically relevant benefit.

NPS PHARMACEUTICALS' teduglutide

The data looked good, but teduglutide generally got little attention from speakers at DDW, who were focused mostly on the biologics. One expert said, "The pilot study looked like it had quite reasonable results. Patients are desperate for stuff that doesn't suppress the immune system. This is intellectually exciting."

Results were presented from an exploratory, 8-week, 100-

Teduglutide Trial Results

Measurement	Placebo n=25	Teduglutide 0.05 mg/kg/day n=24	Teduglutide 0.10 mg/kg/day n=26	Teduglutide 0.20 mg/kg/day n=25
Mean age	39	39	41	42
Baseline CRP	8.9	23.7	17.3	14.6
Primary endpoint: Remission at Week 8 (CDAI<150)	33.3%	~39%	~33%	~57%
>100 decrease in CDAI from baseline at Week 2	29.2%	~25.0%	36.8%	52.6%
>100 decrease in CDAI from baseline at Week 8	57.1%	55.6%	46.7%	61.1%
Change in liquid bowel movements at Week 8	Down ~13%	Down ~13%	Down ~16%	Down ~22%
Safety				
Abdominal pain	11%	6%	16%	8%
Nausea and/or vomiting	6%	3%	6%	5%
Injection site erythema	0	2%	3%	7%
Injection site pain	1	3%	2%	3%
Serious adverse events related to teduglutide	---	0	0	0

patient, double-blind, placebo-controlled trial of teduglutide, an enzyme-resistant GLP-2 analog that addresses mucosal healing as well as mucosal inflammation, in patients with moderate-to-severe Crohn's. Teduglutide was administered once-daily by subcutaneous injection. Researchers reported that 53% of the teduglutide patients responded after two weeks, and 37% experienced remission at the same time. After the full eight week regimen, researchers reported a clinical response in 61% of the treated group and remission in 56%.

UCB Pharma's Cimzia (certolizumab pegol, CDP-870)

The 26-week, placebo-controlled, multi-center, Phase III PRECiSE-1 trial found this subcutaneous humanized monoclonal antibody is effective and well-tolerated in moderate-to-severe Crohn's patients, with a consistent benefit across all treatment subgroups, with many independently significant. The patients received 400 mg certolizumab pegol – a pegylated Fab' fragment of a TNF inhibitor – or placebo at Weeks 0, 2, 4, and then every four weeks until Week 24. The patients were divided into two groups according to their baseline C-reactive protein levels and immunosuppressant/corticosteroid use.

A doctor questioned an expert about the results: "It looks like the six-month results are comparable to trials of other TNF inhibitors, but the shorter-term results don't look as good. Should we tell patients this is slower acting but will get there?" The speaker responded, "A higher dose and more frequent dosing is being explored in RA, and if that is superior, I expect it will be explored in Crohn's…I can't say, looking across trials, that this is less effective at induction than other drugs in the class…This is a 100 point change, and the response change you are used to is a 70 point change…And the other TNF inhibitor trials were in TNF-naïve patients…and we see that response rates are lower in previous TNF responders…So, when you take all factors into account, I think it is difficult to say anything except that this drug is effective in inducing remission."

Asked if it is important to consider CRP levels when considering Cimzia, an expert said, "I should have brought a hat today so I could eat it. I took a public position at a previous DDW meeting that CRP seems important…I think now…that there is no difference in high CRP. I guess I would stop short of saying that CRP has no role, but it doesn't seem to be very important."

PRECiSE-1 Trial of Cimzia in Crohn's Disease

Measurement	ITT		Patients with baseline CRP≥10 mg/L	
	Cimzia 400 mg n=331	Placebo n=328	Cimzia 400 mg n=146	Placebo n=156
CDAI decrease ≥100 from baseline (clinical response) at Week 6	***Primary endpoint #1:*** 35.2% *	26.8%	37.2% *	26.0%
CDAI decrease ≥100 from baseline (clinical response) at Weeks 6 ***and*** 26	23.1% *	16.0%	***Primary endpoint #2:*** 21.5% *	12.3%
CDAI decrease ≥70 points from baseline at Week 6	46.2% *	37.8%	46.9% *	33.1%
CDAI decrease ≥70 points from baseline at Week 6 ***and*** 26	32.0% *	22.5%	29.2% *	14.9%
Remission (CDAI≤150) at Week 6	21.6%	17.2%	21.9%	16.9%
Remission (CDAI≤150) at Weeks 6 ***and*** 26	14.4%	9.8%	13.1%	8.4%
Median CRP by LOCF at Week 6	4.0 mg/L	9.0 mg/L	13.5 mg/L	23.0 mg/L
Median CRP by LOCF at Week 26	4.0 mg/L	9.0 mg/L	15.0 mg/L	27.0 mg/L
Serious infections	7 patients	3 patients	---	---

* p<.05

A study by UCB researchers compared the ability of Remicade, Humira, and Cimzia to neutralize signaling instigated by the binding of soluble and membrane TNF-α to the human p55 receptor. The study found Cimzia has a higher affinity for solution TNF-α and was more potent than Humira and Remicade at neutralizing the signaling by soluble TNF-α. All three anti-TNF agents were equally potent at neutralizing membrane TNF-α signaling through the p55 receptor.

Ulcerative Colitis (UC)

Oral and topical 5-ASA (5-aminosalicylic acid), such as sulfasalazine, olsalazine, balasalazide, and mesalamine, are commonly used first-line to treat **mild UC**. Response rates range from 55%-75% with ≥4 g/day, and remission rates range from 27%-48% with 4 g/day. A speaker said he goes as high as 6-8 g/day in some cases. There are no data on switching from one 5-ASA to another, but an expert said he's found switching can produce responses in some patients.

While mesalamine works for ulcerative colitis, experts emphasized repeatedly that it doesn't work for Crohn's disease – even though it is widely used for that. An expert said, "Mesalamine definitely works for ulcerative colitis, but probably not for Crohn's. In the 20% of Crohn's that 'acts' like ulcerative colitis, mesalamine probably does work."

For **moderate UC**, doctors generally turn to immuno-modulators – azathioprine, 6-mercaptopurine (6-MP), metho-trexate (MTX) – or systemic corticosteroids. Short-term steroid use is beneficial, but long-term use is problematic. At one session, about half the audience indicated they have used MTX, prompting a speaker to comment, "More of you are getting the message that this drug works…In the past it was about 10% of the audience…This is an excellent medication."

For **severe UC**, the options are cyclosporine, Remicade, and surgery. As with Crohn's disease, Remicade is the only FDA-approved biologic at this time. Dr. William Sandborn of the Mayo Clinic predicted Remicade, Humira, and Cimzia will all work in ulcerative colitis as well as Crohn's disease. He said, "(Since) all three work in Crohn's, the trials will eventually show that all three drugs work in ulcerative colitis… Certolizumab missed its (clinical trial) primary endpoint, but there is pretty good evidence of efficacy." Another expert said TNF inhibitors can be helpful as rescue therapy but have little benefit in severe or fulminating colitis, "A small open-label study from the University of Pittsburgh looked at infliximab use in patients with serious colitis. They found 25% of patients responded, with 75% still requiring a colectomy within three months…I would not take infliximab out of the armamentarium, but for out patients it doesn't seem very effective."

Investigational agents for hospitalized patients include:

- **PDL Pharma's Nuvion (visilizumab).**
- **Novartis's Simulect (basiliximab),** an anti-CD-25 that is FDA-approved for renal transplantation.

Antibe Therapeutics' ATB-429

This hydrogen sulfide-releasing derivative of mesalamine is just entering Phase I for Crohn's disease and ulcerative colitis. Researchers from Italy reported that it is more effective than mesalamine in protecting against colitis development in mice.

Proctor & Gamble's Asacol (mesalamine)

P&G is working on an 800 mg formulation that would lower the pill burden for patients to 3 pills BID (6/day). A company official denied that manufacturing issues are holding up this formulation, saying they are making changes to improve it.

Shire's Mesavance (mesalamine, SPD-476)

Shire filed this new formulation of mesalamine with the FDA for UC on December 22, 2005. It is sold as a BID agent in Europe by Ferring as Pentasa. Mesavance would lower the pill burden to two pills (sachets) once a day, instead of the 8-16 pills a day that some patients currently have to take with other products. Doctors agreed that once-daily dosing has the potential to increase compliance and, therefore, overall treatment response, but there does not appear to be a dose response to Mesavance above 2.4 mg/day. A New England doctor said, "Some patients swear by it. It isn't as totally useless (in IBS) as some experts say."

Obesity

Over the past decade there has been an exponential growth in bariatric surgery. In 1998, there were 6.4 operations per 100,000 adults. By 2002, the number had grown to 32.7 per 100,000.

The majority of these procedures continue to be Roux-en-Y. A speaker noted that in 2004, gastric bypass (Roux-en-Y) accounted for 66% of procedures, gastric bands (e.g., Allergan/Inamed's Lap-Band) for 24%, vertical gastric banding (VGB) for 5%, and biliopancreatic diversion (BPD) with or without duodenal switch (DS) for 5%.

Patients lose weight with all of these procedures, but they lose weight faster with gastric bypass than with gastric bands. Proponents of BPD ± DS use it as the procedure of choice in all primary bariatric cases, but other surgeons reserve it for the more severely obese patients (those with a BMI >50-55).

Experts said the outlook is for decreased use of Allergan/Inamed's Lap-Band in Europe and flat to slightly increased use in the U.S. An Ohio surgeon said, "Europeans are a little disenchanted with Lap-Band. There is a low complication rate, but there is a fairly consistent complication rate. In the U.S., there may still be some growth, but it has kind of plateaued. We are putting in fewer than we used to because patients take a lot of maintenance and because of the small but consistent complication rate…The gastric balloon will be approved, and that is a good way to determine who would be a good surgical candidate…And Power Medical Interventions' SurgAssist transgastric stapler is interesting." Another doctor said, "The patient I had with a balloon had terrible halitosis." A California doctor said, "I do mostly Roux-en-Y. Lap-Band use is flat or increasing a little. In a year, it may increase 4%; it will be five years before there is much growth in Lap-Band. There needs to be a culture shift to

adopt Lap-Band. Most fellows are still learning Roux-en-Y, and Lap-Band is becoming dominant in a few centers. The safety issue really drives Lap-Band.

Complications

All the bariatric surgery procedures also are associated with the usual complications of major surgery – wound infections, leakage from the sutures/staples, etc. With banding, the most common problem is anterior gastric prolapse, but gastric perforations, though rare, can occur. However, a speaker emphasized two other complications: biliopancreatic limb obstruction, which is a life-threatening emergency, and malnutrition, including vitamin A and D deficiency. He said, "Secondary HPT (hyperparathyroidism) is common after bariatric surgery. It is rarely clinically obvious, but it is easily correctable by oral supplementation and sunlight exposure… When we looked at our data on the first 500 patients, 60% developed secondary HPT after bypass…Persistent vomiting can occur with any of these procedures, but especially with bands, and it is sometimes associated with thiamin deficiency." Another speaker said, "Wound infections have been drastically reduced with introduction of the laparoscopic approach."

Gastric bands

Dr. Jeff Allen, a professor of surgery at the University of Louisville, reviewed gastric bands. He said one reason they've been "a little slow to catch on" is the speed of the weight loss, "Gastric bypass is much quicker, but one problem is weight regained with that. Americans also are not keen to accept non-U.S. data (on Lap-Bands)…I do both bands and bypasses, about 50/50…(Another expert) does both but more bypass than bands. One of the problems is when I talk to patients, I give them a lot of sovereignty. The band is much safer in the long-run, but there are a lot of downsides: Patients have to come back for frequent adjustments (7 in the first year), and it is purely restrictive. If you are a liquid eater, it doesn't work; bands love ice cream. I can't look at a really heavy person and tell them which is best…If I had a choice, I'd do bands on everyone. Bands are increasing in market share; they are increasing at a higher rate than gastric bypass. I can't predict which will do best for a patient, but in the super-obese (BMI >60) and diabetic patients, bypass will do a little better. And insurance can be an issue."

He cited U.S. data which showed patients losing 48%-87% of their excess weight over time – 44.3% at 12 months in one study, and 64.3% at four years in another – and an Australian study where patients lost 87.2% of their excess weight at two years. Among the other benefits he cited for Lap-Band surgery were: an improvement in metabolic syndrome, a reduction in sleep apnea, a reduction in hypertension.

Dr. Allen insisted that gastric banding is 10 times safer than gastric bypass, but he admitted the weight loss is slower, "Why doesn't everyone have a band? It is not as effective on the super-obese, not as effective in adult onset diabetes, and not as fast."

Occasionally, a band has to be removed, and some doctors are doing that endoscopically. Some of the reasons for explants are: abscess formation, sepsis, obstruction, dilation, prolapse, erosions, and excessive weight loss.

Gastric bypass (Roux-en-Y)

The safety of bariatric surgery came into question with two published reports, one in 2004 and another in 2005, but a speaker cited a retrospective chart review of 40 consecutive cases at University HealthSystems Consortium-affiliated centers, which found the surgery is safe, even at a national level, with sustained weight loss, an improvement in comorbidities and quality of life, and a low rate of complications.

University HealthSystems Consortium Bariatric Surgery Safety Analysis

Measurement	Gastric bypass n=1,049	Restrictive procedures n=94
Mean BMI	49	45
Female	82.4%	71.3%
Laparoscopic procedures	75.7%	91.5%
30-day mortality	0.4%	0
Overall complications	16.0%	3.2%
Wound infection	2.6%	1.1%
Re-operation rate	4.0%	0
30-day hospital readmission	6.6%	4.3%
In-hospital mortality	0.2%	0

Bypass Complications

Complication	Estimated incidence
Mortality	0.5%
Anastomotic leak	1%
CVT/PE	1%
Bleeding	3%
Internal hernia	3%
Wound infection	5%

Vitamin Deficiency with Gastric Bypass

Procedure	Iron	B-12	Calcium	Vitamin D	Vitamin A	Thiamin deficiency
Roux-en-Y	++	++	+++	+	Rare	Rare
Adjustable gastric banding	– –	–	–	–	–	±
Sleeve resection	–	±	–	–	–	Rare
Biliopancreatic diversion	+++	++	+++	+++	+++	+++

New treatments on the horizon

- **Stomal reduction.** A speaker said this is a hot topic, but there is currently less interest in injection modalities.
- **Gastric pouch dilatation (GPD),** which was described as in a "very investigational" stage.
- **Sclerosants.**
- **Suturing techniques.** The speaker said what hasn't been worked out is the impact on weight gain of shrinking the stomach down.
- **Intragastric balloon.** Allergan/Inamed's BioEnterics Intragastric Balloon (BIB) System is not yet FDA approved. The speaker said it is being used in Europe and South America, describing it as easy to do, "Migration of the balloon is what killed the first generation (device)…It was very uncomfortable for patients…It is used for patients too obese to be operated on safely…It is a way to make them able to have surgery."
- **Endolaparoscopic intragastric partitioning.** The speaker said, "The problem with this is it is very hard to sew the stomach…So far, eventually these things have given way."
- **Flexible surgical stapler.** There is a commercial stapler, and "people are trying to figure out an endoscopic way to use it for (gastric) bypass."
- **Transgastric vagal stimulation.** Cyberonics is working on a device to suppress appetite. The speaker said it has shown "some limited benefit" and can be done endoscopically.
- **Endoluminal suturing.** Essentially, this is replicating a laparoscopic sleeve resection. A couple of companies are reportedly in clinical trials outside the U.S. The speaker said the issue is that the stomach is very resistant to tissue apposition; mucosa-to-mucosa apposition doesn't result in healing, so this approach "needs work."
- **Clamping/stapling.**
- **Sealants and stent variations,** including a funnel with a mylar bypass with a stent at the pylorus. This is actively in clinical trials.
- **A malabsorption device.** This mylar device is 100-150 cm in length and is designed to prevent the stomach from absorbing nutrients.
- **Sewing machine.** The speaker said a feasibility study was published years ago, and this is still being worked on, "The stomach is hard to sew together and if you do get it together, it is hard to keep it together."

Gastric bypass surgery candidates may increase

A Mayo Clinic study found that gastric bypass surgery is safe for both adolescents (age 12-18) and elderly patients (age 60-76) who are morbidly obese. Researchers evaluated the long-term risks of a particular type of gastric surgery, Roux-en-Y, in which the stomach is separated into two parts, with the smaller part (or pouch) receiving food intake. That food pouch is then connected to the small intestine to create a new gastric outlet. By searching their database, researchers identified 167 patients who had had the procedure and contacted them to see how they have done since the surgery. The senior study author, Dr. Michael Sarr, said, "This study reveals that bariatric surgery is a safe and effective option for all ages."

Long-Term Results of Roux-en-Y Gastric Bypass Surgery

Measurement	Adolescents at 3 years n=12	Elderly at 5 years n=155
Change in BMI	Down 21 points (from 55 to 34)	Down 13 points (from 46 to 33)
Reduction in obesity-induced diseases and health conditions	Down 82%	Down 51%
30-day mortality	0	0.7%
Serious morbidity delaying hospital discharge	0	14% (6 wound infections, 1 seroma, 5 bowel obstructions, 4 respiratory or CV events, 3 anastomotic leaks, etc.)
Long-term mortality	0 at 3 years	6% at 5 years
Complications	0	15%
Subjective overall patient satisfaction rate	83%	89%

PANCREATIC ENZYMES

Several pancreatic enzymes are sold today that pre-date the FDA approval process – Johnson & Johnson's Pancrease, Solvay's Creon, and Axcan's Ultrase. The FDA has notified each of these companies that they must apply for an NDA and be granted approval by April 2008, or their product will have to be withdrawn from the market. Solvay and Axcan are in a race to do just that.

A Solvay official said his company has the two Phase III trials underway that the FDA requested, and they hope to have approval by 2007. He said, "We want to be first, ahead of Axcan. The FDA required two trials, and they are running now."

Johnson & Johnson may have given up on Pancrease. There was no sign-age for the product at DDW and no staff members able to talk about it.

♦