Dyspepsia
Prevalence in industrialized countries

- worldwide 25% (7 - 41%)
- with heartburn: 40%
- without heartburn & IBS: 10%

Defining Clinical Pathways for Dyspepsia …
… discriminate Dyspepsia from GERD and IBS
(Functional) Dyspepsia, GERD, IBS

*Discrimination by Symptoms limited by Overlap*

- **Abdominal Pain**
- **Diarrhoe**
- **Nausea**
- **Early Sateity**
- **Vomiting**
- **Meteorims**
- **Abdominal Pain**
- **Constipation**
- **Diarrhoe**
- **Distension**
- **Belching**
- **Regurgitation**
- **Epigastric Pain**
- **Bloating**
- **Dysphagia**
- **Heartburn**

Defining Clinical Pathways for Dyspepsia …

Investigated versus Non-investigated Dyspepsia

Upper GI complaints

GERD

Dyspepsia

Lower GI complaints

Irritable Bowel Syndrome

Non-investigated Dyspepsia

Investigated Dyspepsia … had upper GI Endoscopy …
Defining Clinical Pathways for Dyspepsia …

*Organic versus Functional Dyspepsia*

Upper GI complaints

- GERD
- Dyspepsia
- Non-investigated Dyspepsia

Lower GI complaints

- Irritable Bowel Syndrome
- Investigated Dyspepsia
  ... *normal upper GI Endoscopy*

Organic Dyspepsia

Functional Dyspepsia
Dyspepsia

Main causes

- Williams 1988 (n = 1386)
- Stanghellini 1996 (n = 1057)
- Heikkinen 1996 (n = 766)
- Thomson 2003 (n = 1040)

% of patients with diagnosis:

- Gastric neoplasia
- Peptic ulcers
- GERD
- Functional Dyspepsia
Functional Dyspepsia

Rome-III Criteria

Rome III:
- No evidence for structural disease
- One or more of:
  - Bothersome postprandial fullness
  - Early satiation
  - Epigastric pain
  - Epigastric burning
- 2 Subgroups:
  - Postprandial distress syndrome
  - Epigastric pain syndrome

Tack, Gastroenterology 2006; 130:1466-79.
Functional Dyspepsia

Rome-III Criteria versus Rome-II Criteria

Rome III:
- No evidence for **structural** disease
- One or more of:  
  - Bothersome postprandial fullness
  - Early satiation
  - Epigastric pain
  - Epigastric burning
- 2 Subgroups:  
  - Postprandial distress syndrome
  - Epigastric pain syndrome

Rome II:
- No evidence of **organic** disease
- Persistent or recurrent upper GI symptoms
- No relief by defecation or associated with the onset of a change in stool behaviour
- 2 Subgroups:  
  - Dysmotility-like dyspepsia
  - Ulcer-like dyspepsia

Talley, Gut 1999; 45 Suppl 2:II37-II42.

Tack, Gastroenterology 2006; 130:1466-79.
Postprandial Distress Syndrome (PDS)
Must include one or both of the following:
• Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times per week*
• Early satiation that prevents finishing a regular meal, at least several times per week*

Epigastric Pain Syndrome (EPS)
Must include all of the following:
• Epigastric pain or burning (at least moderate severity, at least once per week)*
• Pain is intermittent*
• Not generalized or localized to other abdominal or chest regions*
• Not relieved by defecation or passage of flatus*
• Not fulfilling criteria for gallbladder and sphincter of Oddi disorders*

Supportive criteria:
• Pain may be of a burning quality but without a retrosternal component*
• Pain is commonly induced or relieved by ingestion of a meal but may occur while fasting*
• PDS syndrome may coexist

*Tack, Gastroenterology 2006; 130:1466-79.
Functional Dyspepsia – Rome-III Criteria
Subgroups – PDS and EPS

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• Upper abdominal bloating or postprandial nausea or excessive belching can be present*
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*longer than 3 months, at least 6 months before diagnosis

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Tack, Gastroenterology 2006; 130:1466-79.
Functional Dyspepsia
Exclusion diagnosis

Dyspeptic complaints
(not investigated dyspepsia)

- Anamnesis, physical examination, laboratory (blood count, CRP, GOT, GPT, gGT, Krea, Lipase), sonography
- Upper endoscopy (duodenal eosinophilia?)
- Lower endoscopy, CT/MRT, x-ray: stomach-gut-passage/Sellink, ERCP, MRCP
  **Testing GI function:**
  - H2 breath tests: Lactose, Fructose, SIBO (Glucose)
  - Gastric function: emptying, accommodation
  - pH-metry, esophageal manometry

Functional Dyspepsia
Pathomechanisms

- Stress, Anxiety, Depression, Sexual abuse, Sleep deprivation
- Increased Visceral Sensitivity
  - Sensory inhibition
  - Increased afferent activity
- ANS Imbalance
- Low Grade Inflammation ± HP Infection
- Reduced Acid Clearance
- Increased Acid Sensitivity
- Motor Activity
- Accommodation

Altered Sensory & Motor Function
Functional Dyspepsia - Visceral Hypersensitivity

Hypersensitivity to mechanic Gastric Stimulation


**Intragastric balloon**

Abdominal discomfort (score) vs Intragastric pressure (mm Hg)

- Controls (n=10)
- Functional Dyspepsia (n=10) * p < 0.05

Bar graph showing:
- Initial Sensation
- Pain

Role of Acid in Functional Dyspepsia

Impaired Acid Clearance & Enhanced Sensitivity

Intragastric infusion of 0.1 N HCl 5ml/min. for 10 minutes

Complaints

Hypersensitive FD-Patients
- Activation of the lateral pain system and frontal inferior gyri at lower distention pressures
- none of the components of the medial pain system are activated
**Functional Dyspepsia - Visceral Hypersensitivity**

**Brain Imaging & pathophysiological Mechanisms**

**Hypersensitive FD-Patients**
- Activation of the lateral pain system and frontal inferior gyri at lower distention pressures
- None of the components of the medial pain system are activated

**Lateral Pain System**
*Localisation, Quality, Intensity*
- Insula
- Periaquaeductal Grey (PAG)
- Primary somato-sensory Cortex (SI)
- Secondary somato-sensory Cortex (SII)

**Medial Pain System**
*Affectivity (e.g. Anxiety, Attention)*
- Anterior Cingulum (ACC)
- Prefrontal Cortex (PFC)

---

**Pain Sensory Pathways**

- Präfrontal Cortex (PFC)
  - Pain Memory, -Response Interpretation
- Anteriores Cingulum (ACC)
  - Attention, Anxiety, Arousal
- Insula
  - Visceral Perception
- Thalamus
- Primary Nociceptor
- Dorsal Horn
- Periaquaeductales Grey (PAG)
  - Pain Inhibition
- SI, SII Visceral Perception

---

Functional Dyspepsia
Pathomechanisms of Visceral Hypersensitivity?

- Altered brain processing of Nociceptive information
- Neuroplastic Changes of Sensory Pathways
- Disturbed descending Modulation of Perception
- Low Grade Inflammation ± HP Infection
- Increased mechanical & chemical Sensitivity
- Increase in mucosal mast cells and / or inflammatory cells
Role of Motility in Functional Dyspepsia

Altered Accommodation & Emptying

Inter-digestive
Accommodation
Emptying

Impaired fundic accommodation → redistribution of food to antrum

Tack J. et al., Current Gastroenterology Reports 2001, 3:503-508
Disturbed Gastric Motility in Functional Dyspepsia

**Options of investigation**

- **Gastric emptying**
  - Scintigraphy
  - C13 breath test
  - fMRI

- **Gastric accommodation**
  - Barostat (invasive)
  - SPECT (radiation exposure)
  - fMRI (non invasive)
Impaired Accommodation in Functional Dyspepsia
Detection by Barostat

Impaired Accommodation in Functional Dyspepsia

Detection by Barostat

Pressure/Volume Curves at Food Ingestion

Healthy Controls

Functional Dyspepsia


Impaired Accommodation in Functional Dyspepsia
Detection by SPECT

Fasted Stomach

Postprandial Stomach


Lunding et al.
Scan J Gastro 2006; 41: 1028
Impaired Accommodation in Functional Dyspepsia
Detection by SPECT

Fasted Stomach

Postprandial Stomach

Healthy

Functional Dyspepsia

Proximal gastric accommodation is impaired

Lunding et al. Scan J Gastro 2006; 41: 1028
Impaired Accommodation in Functional Dyspepsia

Detection by SPECT

- Fasted Stomach
- Postprandial Stomach
- Healthy
- Functional Dyspepsia

Proximal gastric accommodation is impaired

Rapid initial emptying of water: a sign of impaired accommodation?


Lunding et al. Scan J Gastro 2006; 41: 1028

Impaired postprandial accommodation to a meal is limited to the proximal stomach

Van der Voort, 2007; in preparation.
Impaired Accommodation and altered Emptying Detection by fMRI – ‘One-Stop Shopping’ ???

More than 50% of patients have one or more alteration in pp relaxation, early or overall gastric emptying

Van der Voort, 2007; in preparation.

Cumulative Change in Volume of the proximal Stomach (ml)

- Functional Dyspepsia (n=22)
- Healthy Controls (n=15)

Patients with one or more Alteration of Accommodation or Emptying (%)

- Impaired accommodation of the proximal stomach
- Initially accelerated gastric emptying
- Impaired relaxation of proximal stomach & initially accelerated gastric emptying
- Delayed overall gastric emptying
- Impaired relaxation of proximal stomach & initially accelerated gastric emptying & delayed overall gastric emptying
- Patients with pathological findings

Impaired postprandial accommodation to a meal is limited to the proximal stomach
Functional Dyspepsia

Pathomechanisms of altered Motility?

- Stress, Anxiety, Depression, Abuse, Sleep deprivation
- ANS Imbalance
- Neuroplastic Changes of Sensory Pathways
- Low Grade Inflammation ± HP Infection

Alteration of neurohumoral duodeno-gastric feedback (CCK)

Motor Activity ↓
Electr. Activity ↓
Accommodation ↓
Emptying ↓
Treatment of Functional Dyspepsia
Basic Measures and Principles

• The treatment of the patient starts with the positive diagnosis (Cave: “...There is nothing wrong....“).

• Education about the benignity of the disease

• Dietetic consultation (Diary: trigger factors?)

• Separate patients with FD from reflux disease!

• Take advantage of the very high placebo effect: „To act or not to act?“ → Be proactive!
Treatment of Functional Dyspepsia

Placebo Effect

Placebo effect in therapeutic studies (different time points)

Meta-analysis

Mean > 40%

Treatment of Functional Dyspepsia

**Lifestyle modifications**

**Recommendations**

- Small frequent meals
- Stop smoking
- Reduce alcohol
- Reduce caffeine
- Avoid irritating food
- Maintain an ideal weight
- Review medications

But:
- Anecdotal reports only
- RCTs are missing

Drug therapy in Functional Dyspepsia
Groups of Compounds and Modes of Action

- **Acid inhibition**  Antacids, H2-blocker, PPI
- **Cytoprotection**  Sucralfate, PG analogues (misoprostol)
- **Prokinetics**  Metoclopramide, Domperidone, (Cisapride)
- **H. pylori eradication**  PPI + antibiotics, bismuth
- **Visceral analgetics**  Opiate agonists, 5-HT₃-R-antagonists
- **Antidepressants**  Amitriptyline, Mianserin
- **Spasmolytics**  Butylscopolamine
- **Antiemetics**  Phenotiazine
- **Herbal medicine**  Iberis amara, peppermint oil, caraway oil
- **Carminatives**  Simethicone
Therapy of Functional Dyspepsia

Acid Inhibition
Drug Treatment of Functional Dyspepsia
Cochrane Meta-Analysis of 73 Studies

Moayyedi p et al., Cochrane Database Syst Rev. 2007; Iss 3
Therapy of Functional Dyspepsia with PPIs

Differences between Subgroups

n = 1248, FD, double blind, placebo-controlled

- Placebo
- Omeprazole 10 mg
- Omeprazole 20 mg

**Therapy with Omeprazole**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Free of Symptoms in %</th>
<th>10 mg</th>
<th>20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer-type</td>
<td>50</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Reflux-type</td>
<td>50</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Dysmotility-type</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05

Therapy of Functional Dyspepsia with PPIs

Differences between Subgroups


Omeprazole 10 mg
Placebo

n = 1248, FD, double blind, placebo-controlled

Omeprazole 20 mg

Free of symptoms in %

Dysmotility-type 50
Ulcer-type 50*
Reflux-type 50*

* p < 0.05

Meta-Analysis


- 7 studies, 3725 patients

- PPI more effective than placebo (RRR = 10.3%, NNT = 14.6)
- Significant effect only in ulcer-like and reflux-like dyspepsia, but not in dysmotility-like & unspecified dyspepsia

Therapy of Functional Dyspepsia

(Pro-)Kinetics
Therapy of Functional Dyspepsia with Prokinetics

Meta-analysis of 27 studies

- 27 Studies, N=3435
  - 1844 Pat. received Drugs
  - 1591 Pat. received Placebo

- 6 Drugs:
  Metoclopramide, Domperidone, Trimebutine, Cisapride, Itopride, Mosapride

The drugs have 30% excess probability of producing a response compared to placebo

### Therapy of Functional Dyspepsia with Prokinetics

**Targets, Agents and Clinical Efficacy**

<table>
<thead>
<tr>
<th>Target</th>
<th>Pharmacodynamics</th>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Clinical efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine receptor</td>
<td>D&lt;sub&gt;2&lt;/sub&gt; antagonistic</td>
<td>Metoclopramide</td>
<td><strong>Acceleration of GE</strong></td>
<td>Benefit shown by limited analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Domperidone</td>
<td><strong>Acceleration of GE</strong></td>
<td>Benefit shown by meta-analysis of a small number of trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levosulpiride</td>
<td><strong>Acceleration of GE</strong></td>
<td>Benefit shown by a randomized trial to be similar to cisapride</td>
</tr>
<tr>
<td>Serotonin receptor</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;/AChE blocker</td>
<td>Ipecac</td>
<td>Modulation of GE &amp; GA</td>
<td>Benefit shown by a placebo-controlled trial</td>
</tr>
<tr>
<td></td>
<td>5-HT&lt;sub&gt;1B&lt;/sub&gt; agonist</td>
<td>Sumatriptan</td>
<td>Modulation of GA</td>
<td>Benefit shown by a placebo-controlled trial</td>
</tr>
<tr>
<td></td>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt; agonist</td>
<td>Buspirone</td>
<td>Modulation of GA</td>
<td>Benefit shown by a placebo-controlled trial</td>
</tr>
<tr>
<td></td>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt; agonist</td>
<td>Alosetron</td>
<td>Reduction of VH</td>
<td>Benefit shown by a placebo-controlled trial</td>
</tr>
<tr>
<td></td>
<td>5-HT&lt;sub&gt;4&lt;/sub&gt; agonist</td>
<td>Cisapride</td>
<td><strong>Acceleration of GE</strong></td>
<td>Benefit shown by meta-analysis of several placebo-controlled trials</td>
</tr>
<tr>
<td>Other receptor</td>
<td>CCK antagonist</td>
<td>Dextroliumide</td>
<td>Modulation of GA &amp; GE</td>
<td>Beneficial tendency shown by limited analysis</td>
</tr>
<tr>
<td></td>
<td>Opioid κ agonist</td>
<td>Fedotozine</td>
<td>Reduction of VH</td>
<td>Variable data (benefit over tegremin by a large randomized trial)</td>
</tr>
<tr>
<td></td>
<td>NMDA antagonist</td>
<td>Dextromethorphan</td>
<td>Reduction of VH</td>
<td>Benefit shown by limited analysis</td>
</tr>
<tr>
<td></td>
<td>NK-1 antagonist</td>
<td>Aprepitant</td>
<td>Reduction of VH</td>
<td>Benefit shown by a placebo-controlled trial</td>
</tr>
<tr>
<td></td>
<td>NK-3 antagonist</td>
<td>Talnetrant</td>
<td>Reduction of VH</td>
<td>Benefit shown by a placebo-controlled trial</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>NO donor</td>
<td>Glyceryl trinitrate</td>
<td>Modulation of GA</td>
<td>No data for FD</td>
</tr>
<tr>
<td></td>
<td>PDE-5 inhibitor</td>
<td>Sildenafil</td>
<td>Modulation of GA</td>
<td>No data for FD</td>
</tr>
<tr>
<td>Others</td>
<td>Kampo medicine</td>
<td>Lin-jun-zhi-tang</td>
<td>Modulation of GA &amp; GA</td>
<td>Benefit shown by limited analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Banxia-houpo-tang</td>
<td>Acceleration of GE</td>
<td>Benefit shown by limited analysis</td>
</tr>
</tbody>
</table>

*Mizuta et al., J Gastroenterol 2006; 41:1025–1040*
## Drug Treatment of Functional Dyspepsia

### Prokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Studies</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisapride</td>
<td>5-HT4-Agonist</td>
<td>+++</td>
<td>several but often small studies (→ publication bias) Cardiac arrhythmias!</td>
</tr>
<tr>
<td>Domperidone</td>
<td>D2-Antagonist</td>
<td>++</td>
<td><strong>Domperidone:</strong> &gt; placebo In 10 of 11 studies</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
<td></td>
<td>Effect in severe gastroparesis</td>
</tr>
<tr>
<td>Tegaserod</td>
<td>5-HT4-Agonist</td>
<td>+</td>
<td>first studies</td>
</tr>
<tr>
<td>Itopride</td>
<td>D2-Antagonist &amp; AChE - Blocker</td>
<td>+</td>
<td>Recent study failed to detect effect on Dyspepsia Index Talley, DDW 2007.</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>SSRI</td>
<td>(+)</td>
<td>first studies</td>
</tr>
</tbody>
</table>
Drug Treatment of Functional Dyspepsia

Tegaserod – Current Experimental Data

Effects of Tegaserod on Gastric Compliance (Basal and pp Condition)

- Enhances accommodation in FD

Influence of Tegaserod on Gastric Accommodation (Introduodenal Lipid)

- Has no effect on gastric visceral sensation

Thusmhirn et al.,
Aliment Pharm Ther 2007; in press
Drug Treatment of Functional Dyspepsia

Tegaserod – Current Clinical Data

• Tegaserod improved Short Form Nepean Dyspepsia Index after 6 weeks treatment in patients with moderate to severe Functional Dyspepsia
  Talley, DDW 2007.

• Difference between placebo and tegaserod in the more severe subgroup of FD patients was more than 10%
  Vekil, DDW 2007.

• Tegaserod improved daily activity impairment in FD patients with a more pronounced effect in patients with more severe symptoms

• Tegaserod was also effective in patients with FD-heartburn overlap

• Tegaserod was well tolerated during 12 months‘ treatment with mild diarrhea being an anticipated adverse event
  Chey, DDW 2007.

IBS trials suggest cardiovascular side effects.
The future of tegaserod for this indication is vague.
Drug Treatment of Functional Dyspepsia

Is Itopride effective in the treatment of FD?

Response Rate (wk 8)

- Placebo
- Itopride 50 mg 3x/d
- Itopride 100 mg 3x/d
- Itopride 200 mg 3x/d

* p < 0.05

Drug Treatment of Functional Dyspepsia

Is Itopride effective in the treatment of FD?

**Response rate**

<table>
<thead>
<tr>
<th>% of patients</th>
<th>Placebo</th>
<th>Itopride 50 mg 3x/d</th>
<th>Itopride 100 mg 3x/d</th>
<th>Itopride 200 mg 3x/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>* p &lt; 0.05</td>
<td>40</td>
<td>60</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

Itopride failed to exert an effect on Nepean Dyspepsia Index in FD (Phase III study)

Talley, DDW 2007.

No effects on:
- gastric emptying
- orocecal transit
- fasting gastric volume
- maximum tolerated volume
- aggregate symptom score at nutrient drink challenge

Choung, Neurogastroenterol Motil 2007; 19:180–18

Therapy of Functional Dyspepsia

Visceral Analgetics & Antidepressants
Hypersensitivity in Functional GI Disorder

Targets of afferent nociceptive Pathways

Cortex

Spinal Cord
- Descending inhibitory fibres
  - ANS. Input
- 2nd order neurons
- Dorsal horn nucleus

Dorsal root ganglion

Sensory nerve endings in gut

Pain Perception

Pharmacological Options
- μ opiates, Tricyclics
- 5HT³ antagonists

Clonidine
- K-opiates
- 5HT³ antagonists

Substance P
- CGRP antagonists

NSAIDs
- K–opiates
- 5HT³ antagonists
Therapy of Functional Dyspepsia - Antidepressants
Effects on abdominal pain

In favor of placebo

Tanum et al., 1996
Song et al., 1989
Arienti et al., 1994
McHardy et al., 1968

In favor of true drugs

Database:
- 13 studies (n=1717)
- Placebo-controlled
- Randomized

Overall (95% CI)
0.55 (0.36-0.85)

Standardized mean difference

Meta-Analysis of 4 placebo-controlled studies with anxiolytics/antidepressants

# Antinociceptive Treatment of Functional Dyspepsia

## Visceral Analgetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Proof in studies</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fedotozine</td>
<td>Peripheral k-Opiate-R-Agonists</td>
<td>+/-</td>
<td>In 2 placebo-controlled studies only low effect</td>
</tr>
<tr>
<td>Asimadoline</td>
<td></td>
<td></td>
<td>A recent study did not show any effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Choung, DDW 2007.</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>5-HT3-Antagonists</td>
<td>?</td>
<td>No clinical studies</td>
</tr>
<tr>
<td>Cilansetron</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mianserin (Antidepressant)</td>
<td>5-HT2,- 5-HT3,-, α2-Antagonist</td>
<td>+/-</td>
<td>In 1 study (heterogen) better than placebo</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>5-HT1-Agonist</td>
<td>+/-</td>
<td>In 1 study significant improvement of pp symptoms</td>
</tr>
</tbody>
</table>
Drug treatment of FD with a 5-HT1-R-Agonist

Sumatriptan enhances gastric accommodation


Effect of the 5HT1-R-Agonist Sumatriptan

Accommodation

Food intake for maximum satiety (kcal)

Symptoms
Treatment of Functional Dyspepsia with SSRIs

Paroxetin - beneficial effects on gastric function?

Mönnikes et al; in preparation.
Therapy of Functional Dyspepsia

H. pylori Eradication
Helicobacter pylori in Functional Dyspepsia

Meta-analysis: Eradication vs. Placebo Eradication

- PPI treatment
- Dichotomous variables
- 17 studies, 3566 patients

- RRR: 10% (CI = 6 - 14%)
- NNT = 14 : 1 (CI = 10 - 25%)

H. pylori Eradication in Functional Dyspepsia

Complete Relieve of Symptoms after 1 Year

4 studies, 487 patients receiving eradication therapy, 491 placebo,
Symptoms/success of eradication after 12 months

Complete Relief of Symptoms in %

* p < 0.05

Wang, DDW 2007.
Therapy of Functional Dyspepsia

Herbal Preparations & Carminatives
Treatment of Functional Dyspepsia with STW 5

Clinical data

3 studies
STW 5 n = 138
Placebo n = 135
Reduction of GI symptoms


Current Meta-analysis:
- Iberogast vs. Placebo
- 4 Studies, n = 637
- Dyspepsia score sig. reduced in the STW 5 group
-NNT = 10
Holtmann, DDW 2007.

<table>
<thead>
<tr>
<th>Clinical trial/surveillance (Indication)</th>
<th>Number of patients treated with STW 5</th>
<th>Number of adverse events assessed to be in possible or probable causal relationship to STW 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 controlled studies (functional dyspepsia)</td>
<td>320</td>
<td>10</td>
</tr>
<tr>
<td>12 open clinical trials, one postmarketing surveillance (gastrointestinal diseases, functional dyspepsia)</td>
<td>2554</td>
<td>10</td>
</tr>
<tr>
<td>2 retrospective surveillances with children up to 12 years (functional gastrointestinal diseases, functional dyspepsia)</td>
<td>42,003</td>
<td>–</td>
</tr>
<tr>
<td>1 retrospective cohort-study (functional dyspepsia)</td>
<td>490</td>
<td>–</td>
</tr>
<tr>
<td>Treated patients in Germany, adverse events (spontaneous reports) since market launch</td>
<td>&gt;20,000,000</td>
<td>18</td>
</tr>
</tbody>
</table>

Herbal medicine in the treatment of FD
Effect of STW 5 on gastric motility

In vitro study

# Drug therapy of Functional Dyspepsia

## Herbal medicine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Proof in studies</th>
<th>Comment</th>
</tr>
</thead>
</table>
| **Iberogast**<sup>®</sup>  
Iberis amara + 8 drug mixed extract | spasmylytic & toning  
carinative?  
antimicrobial? | +                 | 2 published placebo-controlled studies, 1 abstract  
1 comparison with Cisapride  
| **Enteroplant**<sup>®</sup>  
Peppermint oil +  
Caraway oil | spasmylytic  
antimeteoristic  
choleretic | +/?              | 2 placebo-controll. Studies  
May, Aliment Pharmacol Ther 2000; 14:1671-7;  
1 comp. with Cisapride  
| **Lipei**<sup>®</sup>  
Artichoke extract | spasmylytic  
choleretic | +/?              | 1 placebo-controlled study  
Holtmann, Aliment Pharmacol Ther 2003; 11-12;  
1099-105. |
| **Cholagogum F**<sup>®</sup>  
Celandine/Curcuma | choleric | +/?              | 1 placebo-controll. study  
„biliary complaints“  
Drug therapy of Functional Dyspepsia – Carminatives

Simethicone has beneficial Effects

Simethicone has beneficial Effects

N=185
- Placebo
- Cisapride, 3x10mg
- Simethicon, 3 x 105 mg

Symptom-Score

Change of Symptom-Score

O’Brein Sum Score normalized Deltas

Week 2  Week 4  Week 8

Therapy of Functional Dyspepsia

Psychotherapy
# Treatment of Functional Dyspepsia

## Psychotherapy

<table>
<thead>
<tr>
<th>Intervention &amp; Outcome criteria (different !)</th>
<th>Evidence</th>
<th>Randomized, controlled Tr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Kognitive Therapy</td>
<td>+</td>
<td>Haug et al. 1994</td>
</tr>
<tr>
<td>• Improvement of epigastric symptoms at 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Psychosocial Support by Group Therapy</td>
<td>+</td>
<td>Bates et al. 1998</td>
</tr>
<tr>
<td>• Decrease in pain intensity and frequency after 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Psycho-dynamic Therapy</td>
<td>+/-</td>
<td>Hamilton et al. 2000</td>
</tr>
<tr>
<td>• Decrease of Dyspepsia Score after 3 (but not 12) Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypnotherapy</td>
<td>+</td>
<td>Calvert et al. 2002</td>
</tr>
<tr>
<td>• Decrease of Dyspepsia Score after 12 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Psychotherapy in Functional Dyspepsia
Enhancing Coping Flexibility

Reduction of self-rated Dyspeptic Symptom Severity

Flexible Coping Psychotherapy (FCP) n = 33
Supportive Psychotherapy (SPP) n = 31

Therapy of Functional Dyspepsia

Drug Pipeline
Drug Pipeline for Therapy of Functional Dyspepsia

Drugs affecting Gastric Emptying

**ATI-7505** (5-HT4-R Agonist)
- accelerated GE and increased colonic transit in healthy subjects (HS)
  *Camilleri, Neurogastroenterol Motil 2007; 19:30-8.*

**ABT-229** (Motilide)
- enhanced GE and stimulated antral motility in healthy subjects#
- failed to relieve symptoms in FD patients*

**Mitemcinal** (= GM-611, Motilin Agonist)
- relieved gastroparesis symptoms in diabetic patients

**Ghrelin** (endogenous GHS)
- enhanced liquid emptying & decreased meal-related symptoms in idiopathic gastroparesis

**Loxiglumide** (CCK-A Antagonist)
- accelerated GE and increased antral motility in HS
  *Borovicka, Gut 1997; 41:500-4.*

**Botulinum Toxin**
- Intrapyloric botulinum toxin sig. enhanced solid but not liquid GE and improved meal-related symptoms in gastroparetic patients
  *Arts, Aliment Pharmacol Ther 2006; 24:661-7.*
Drug Pipeline for Therapy of Functional Dyspepsia

Drugs targeting at Gastric Emptying

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- accelerated GE and increased colonic transit in healthy subjects (HS)

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  Arts, Aliment Pharmacol Ther 2006; 24:661-7.

- Significant Effects in Functional Dyspepsia in general have not been proven so far

- Improvement of Symptoms in Patients with Gastroparesis

→ Test Gastric Emptying in Patients with Functional Dyspepsia!
Drug Pipeline for Therapy of Functional Dyspepsia

Drugs targeting at Visceral Hypersensitivity

Capsaicin (major component of red pepper, binds to vanilloid receptors)
- did not affect dyspeptic symptoms in patients with heartburn #
  - Red pepper over a period of 5 weeks reduced the overall symptom score as well as epigastric pain, fullness, and nausea in FD patients*

Talnetan (Neurokinin 3-R Antagonist)
- reduced nociception associated with colorectal distention and stress-induced hypersensitivity in rats

Asimadoline (Peripheral κ-Opiate-R-Agonists)
- no effect in functional dyspepsia
  Choung, DDW 2007.

Clonidine (α2-adrenergic agonist & nitrenergic control of smooth muscle)
- relaxes the stomach and reduces gastric sensation without inhibiting accommodation or emptying in healthy volunteers.
Drug Pipeline for Therapy of Functional Dyspepsia

Drugs targeting at Fundus Relaxation

**Sildenafil** (Phosphodiesterase-5 Inhibitor)
- increased fasting intragastric volume and volume of first perception; induced a high postprandial relaxation and slowed liquid emptying in healthy subjects
  
  *Sarnelli, AJP Gastrointest Liver Physiol 2004; 287:G988-G92.*

**Buspirone** (5-HT-1a-R Agonist)
- enhanced gastric accommodation and improved symptoms in FD
  

**R137696** (5-HT-1a-R Agonist)
- increased proximal stomach volume but did not affect distention-evoked dyspeptic symptoms in healthy subjects
  
  *Boeckxstaens, Neurogastroenterol Motil 2006; 18:919-26.*

**Z-338** (muscarinic M1 and M2 autoreceptors blocker → ACh release)
- enhances GI motility, gastric emptying and fundus relaxation
- ongoing international multicenter study
  
  *Ogishima,JPET 294:33-37,*
Dyspepsia
Subgroups in the Population

Factor Analysis → Questionnaire → Population

Drug Therapy in Functional dyspepsia

**Targeting Symptoms**

- **Early Satiety**
- **Fullness**
- **Pain**
- **Nausea**
- **Vomiting**

**Proton pump inhibitors**

**Spasmolytics**

**STW 5**

**(5-HT4-Agonists)**

**Simethicone**

**SSRIs**

**Metoclopramide**

**TCA**

**HP eradication**

**Antiemetics**

**Abdominal bloating**
Thank you
Functional Dyspepsia
Management

Drug therapy necessary?

Education, individual diet

EPS: Antisecretory: PPI
PDS: Prokinetic: Domperidone

Re-evaluation after 4 weeks

Success: Stop of medication
Failure: Change on alternative therapy
Failure: Clin. re-evaluation
Success: Stop of medication

Monitoring

Individual applicable therapy options a.o.:
- Antidepressants: Refractory symptoms, Constant Pain
- Eradication: Request of patient, NSARD therapy
- Herbal medicine: Postprandial Disstress Syndrome
- Psychotherapy: Refractory symptoms, QoL
Non-investigated Dyspepsia
Pathways of Patient Management

Age > 45 years
- Alarm Symptoms
  - Risk of Malignancy
  - Endoscopy (EGD)
  - Biopsy for HP-Test

Age ≤ 45 years; no NSRAs
- No Alarm Symptoms
  - HP Prevalence < 10%
    - PPI empirical
    - Test & treat for HP
    - Endoscopy (EGD)
  - HP Prevalence ≥ 10%
    - Test & treat for HP
    - PPI empirical
    - Endoscopy (EGD)
GERD: Comparison of symptoms and pH-metry

Typical symptoms are specific but not sensitive

- Odynphagia
- Pharyngeal Pain
- Sickness
- Belching
- Upper Abdominal Pain
- Retrosternal Pain

- Retrosternal Burning
- Acid Regurgitation
- Heartburn

Patients with typical symptoms ~ 50% have non-excessive reflux

With excessive reflux: also report non-typical and extra-esophageal symptoms

Klauser et al., Lancet 1990; 335:205-208
Dyspepsia, GERD, IBS

Discrimination by Symptoms limited by Overlap

Falk Symposium

Functional Dyspepsia

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