

Beyond Acid - Suppressive Medications – Neuromodulators and Behavior Modification

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Definitions of Nonerosive Reflux Disease (NERD)

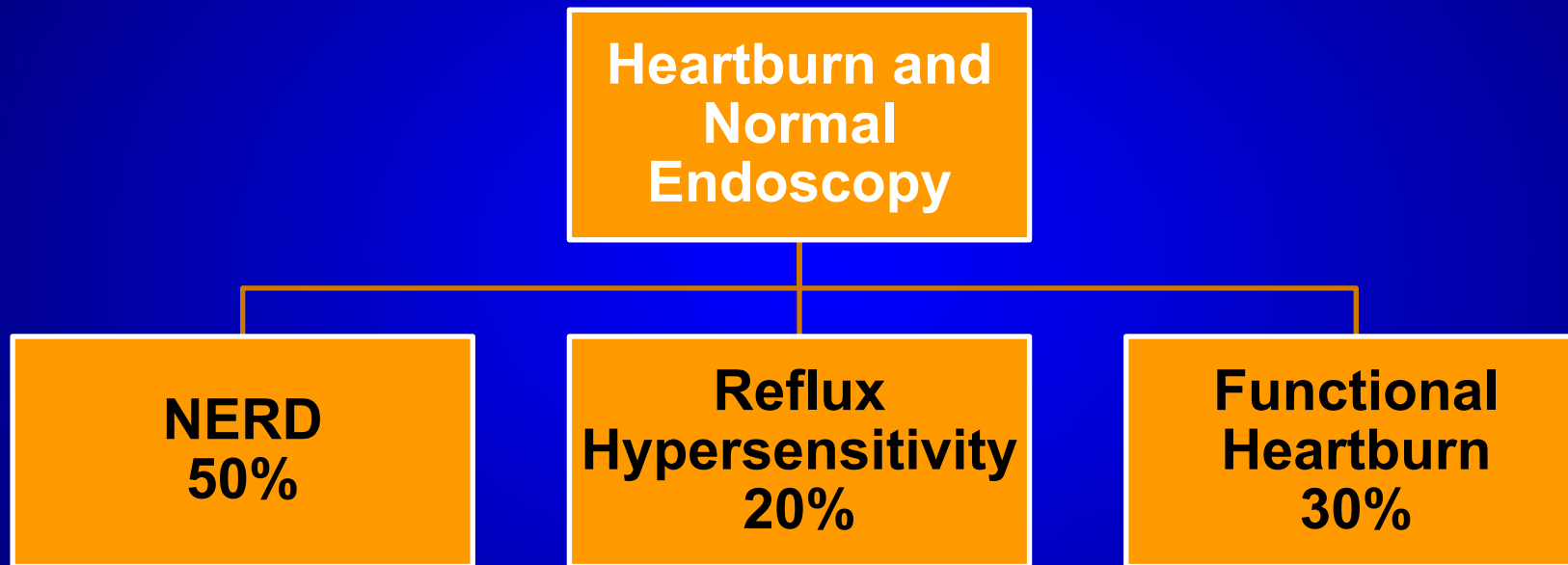
Montreal Consensus - “Nonerosive reflux disease is defined by the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks.”

Vevey Consensus - a subcategory of GERD characterized by troublesome reflux-related symptoms in the absence of esophageal mucosal erosions/breaks at conventional endoscopy and without recent acid-suppressive therapy.

Vakil *et al.* *Am J Gastroenterol* 2006;101:1900-1920.

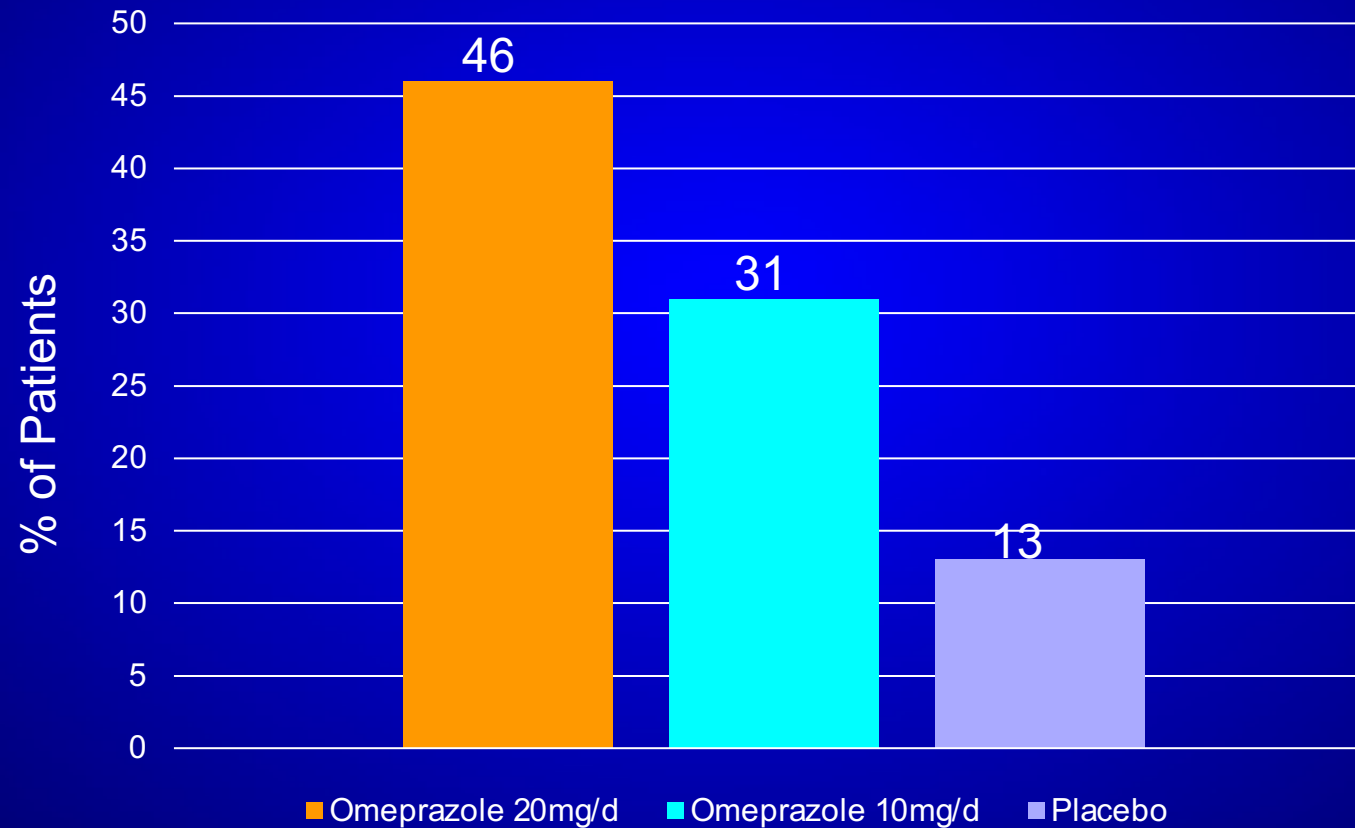
Modlin IM *et al.* *Digestion.* 2009 Oct; 80(2): 74–8

Who Are The Patients With Heartburn And Normal Endoscopy?

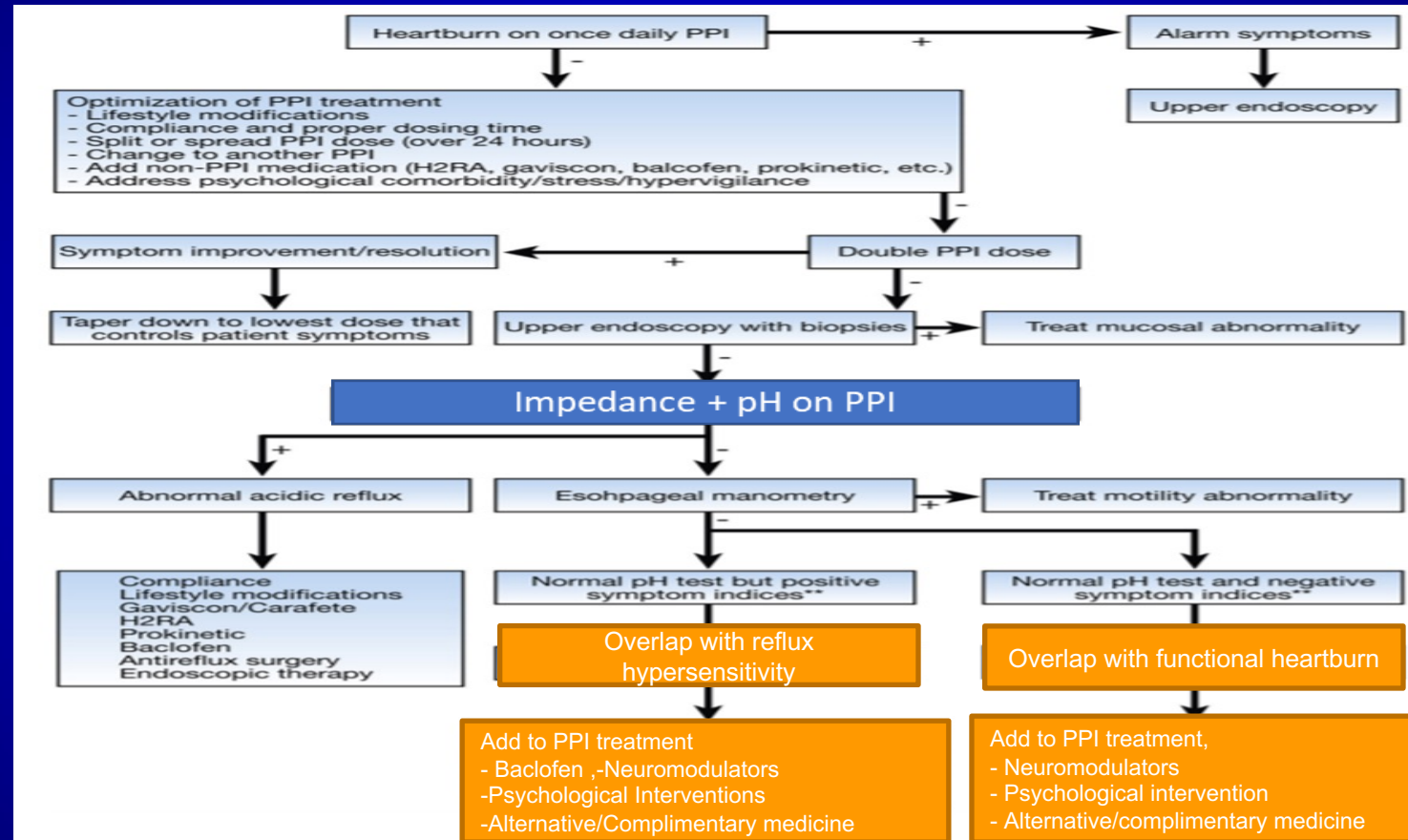


Proportion of NERD Patients Responding to Treatment at 4 Weeks

N = 509



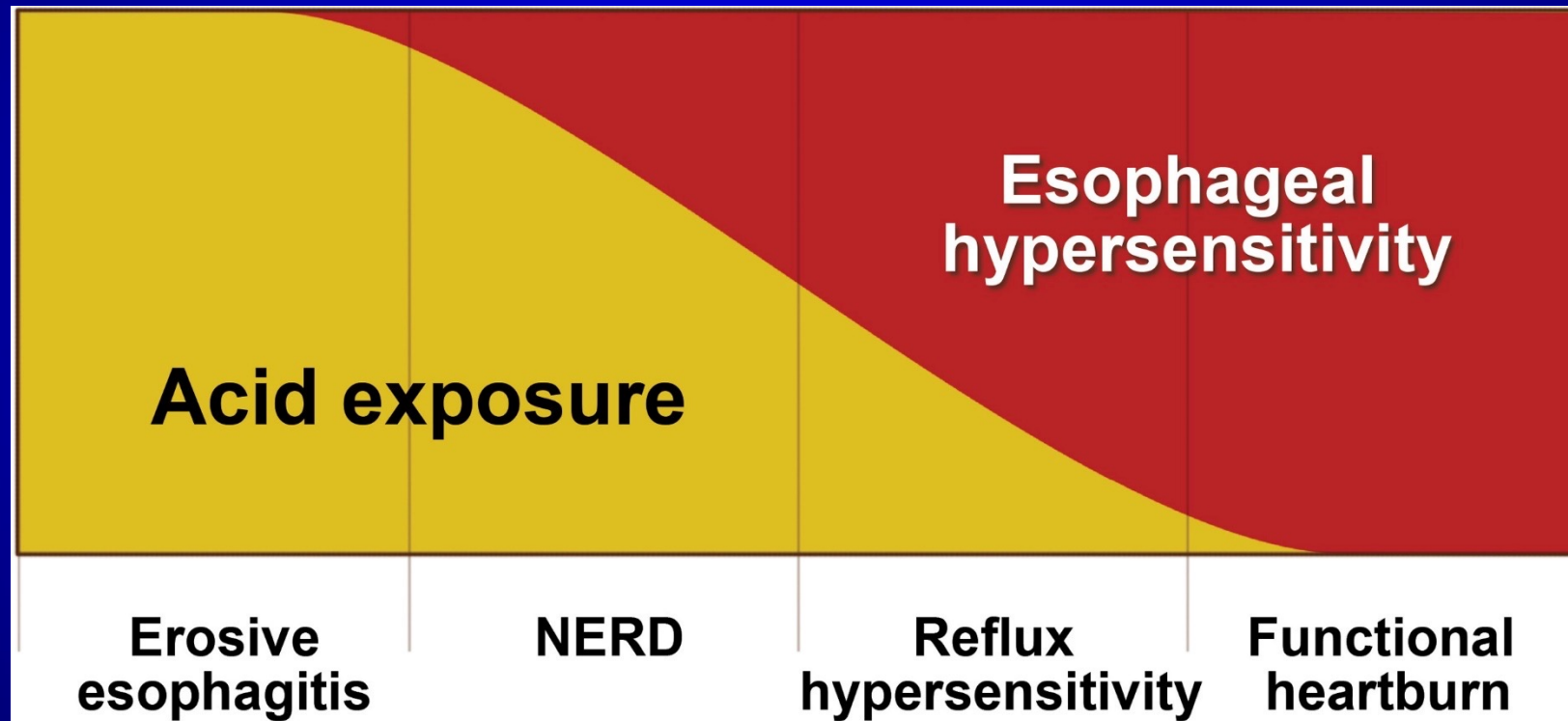
Management Algorithm of Patients With Refractory GERD



Phenotypes of GERD Patients With Persistent Symptoms

1. Breakthrough Acid With Large Hiatal Hernia
2. Breakthrough Acid With Small/Absent Hiatal Hernia
3. Reflux Hypersensitivity to Heartburn With Large Hiatal Hernia
4. Reflux Hypersensitivity to Regurgitation With Large Hiatal Hernia
5. Reflux Hypersensitivity to Heartburn With Small/Absent Hernia
6. Reflux Hypersensitivity to Regurgitation With Small/Absent Hiatal Hernia
7. Elevated Reflux Burden With Large Hiatal Hernia
8. Elevated Reflux Burden With Small/Absent Hiatal Hernia
9. Negative testing

The Interplay Between Esophageal Hypersensitivity and Acid Exposure in the Different Heartburn Groups



Neuromodulators

- Antidepressants: TCA's, SSRIs, SNRIs and Trazodone
- Adenosine agonists: Theophylline
- Serotonin agonists and antagonists: Tegaserod
- Antiepileptics: Pregabalin
- Peripheral neuropathy analgesics: Gabapentin
- Histamine 2 receptor antagonists: Ranitidine

Hierarchy of Antidepressants for Esophageal Pain Reduction and Global Health Improvement

Pain Reduction	Global Health Improvement
1. Venlafaxine	1. Venlafaxine
2. Sertraline	2. Sertraline
3. Imipramine	3. Trazodone
4. Trazodone	4. Imipramine
5. Paroxetine	5. Paroxetine

Psychological Interventions

- CBT
- Hypnotherapy
- Multi-component
psychological therapy
- Dynamic psychotherapy
- Mindfulness

AGA Clinical Practice Update: Functional Heartburn

- Proton pump inhibitors have no therapeutic value in functional heartburn, the exception being proven GERD that overlaps with functional heartburn
- Neuromodulators, including tricyclic antidepressants, selective serotonin reuptake inhibitors, tegaserod and histamine-2 receptor antagonists can be used as primary therapy in functional heartburn or as add on therapy in functional heartburn that overlaps with proven GERD
- Acupuncture and hypnotherapy may have a role as sole treatment of functional heartburn, or in conjunction with another therapeutic modality.
- Anti-reflux surgery and endoscopic GERD treatment modalities have no therapeutic role in functional heartburn.

Randomized Controlled Trials (RCTs) Of Neuromodulators In Functional Esophageal Disorders

Name	Class of drugs	Disorder	Dose	Response rate	Side effects
Imipramine ¹⁶¹	TCAs	NCCP	50 mg/d	52%	QT prolongation
Imipramine ¹⁶²	TCAs	NCCP	50 mg/d	Significant	Dry mouth, dizziness
Imipramine ¹⁶³	TCAs	FH, RH	25 mg/d	37.2%	Constipation
Amitriptyline ^{164,165}	TCAs	NCCP, globus	10,25 mg/d	52%, significant	Excessive sleeping, dizziness
Sertraline ¹⁶⁶	SSRIs	NCCP	50–200 mg/d	57%	Nausea, restlessness
Sertraline ¹⁶⁷	SSRIs	NCCP	50–200 mg/d	Modest	Dry mouth, diarrhea
Paroxetine ¹⁶⁸	SSRIs	NCCP	10–50 mg/d	Modest	Fatigue, dizziness
Paroxetine ¹⁶⁹	SSRIs	NCCP	10–50 mg/d	21.7%	None
Citalopram ¹⁷⁰	SSRIs	RH	20 mg/d	Significant	None
Fluoxetine ¹⁷¹	SSRIs	FH/RH	20 mg/d	Significant	Headache, dry mouth
Trazodone ¹⁶⁰	SRI	Dysmotility	100–150 mg/d	29%–41%	Dry mouth, dizziness
Venlafaxine ¹⁷²	SNRIs	NCCP	75 mg/d	52%	Sleep disturbances
Ranitidine ¹⁷⁶	H2RAs	FH	300 mg/d	Significant	None
Theophylline ¹⁷³	Adenosine antagonists	NCCP	200 mg twice per d	58%	Nausea, insomnia, tremor
Gabapentin ¹⁷⁴	GABA analog	Globus	300 mg 3 times per d	66%	None

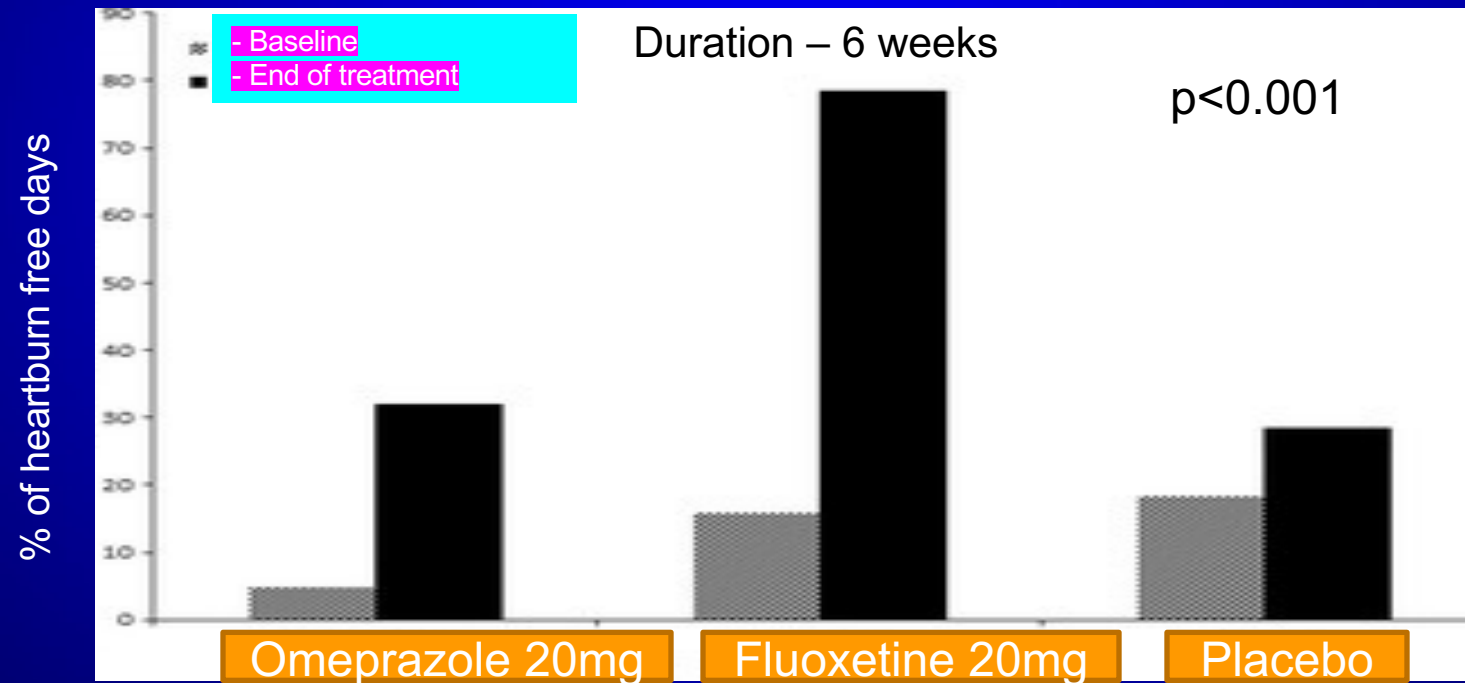
FH, functional heartburn; GABA, gamma-aminobutyric acid; NCCP, noncardiac chest pain; RH, reflux hypersensitivity; SNRIs, serotonin-norepinephrine reuptake inhibitors; SRI, serotonin reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Esophageal Balloon Distention Sensory Variables After 14 Days of Treatment With 6 mg of Tegaserod Twice Daily or Placebo (N=42)

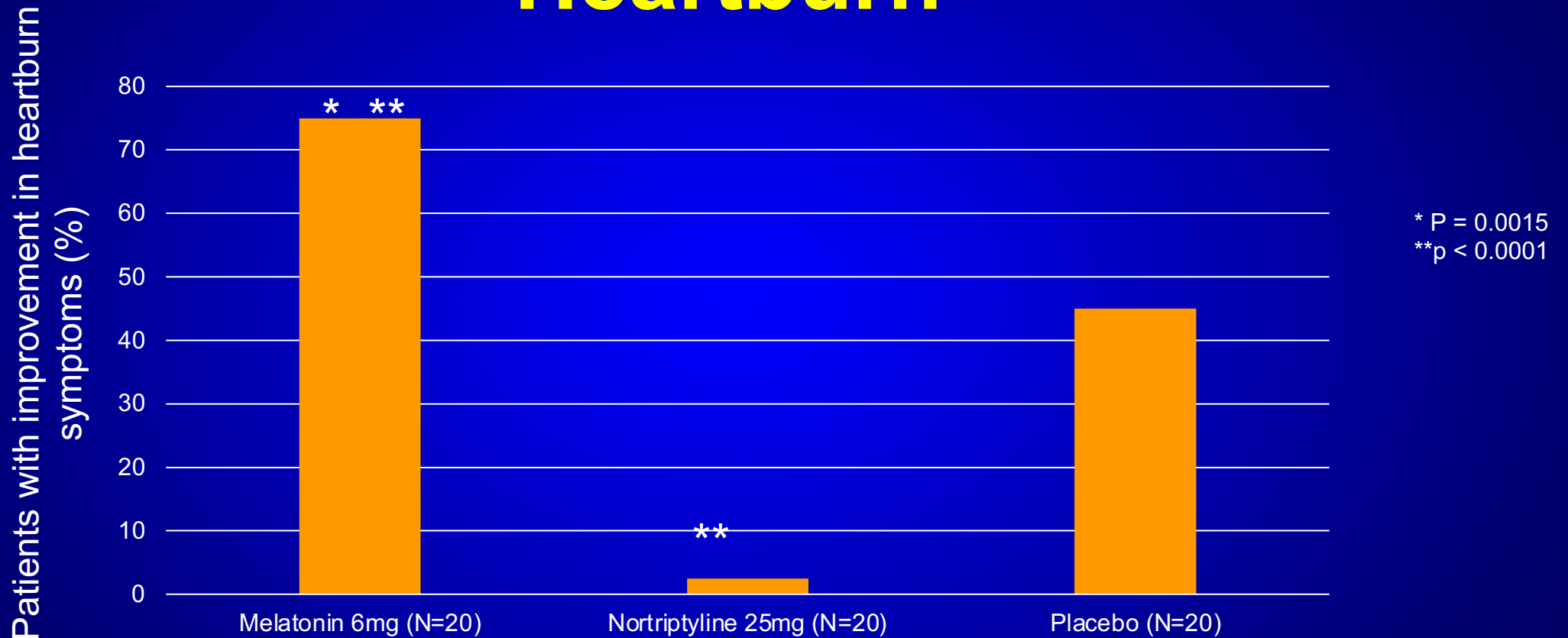
Variable	6 mg Tegaserod twice daily		Placebo		P value
	n	Mean ± SD	n	Mean ± SD	
Balloon pressure at first sensation (<i>mm Hg</i>), ramp	42	5.37 ± 3.41	42	5.82 ± 4.37	.543
Balloon pressure at pain (<i>mm Hg</i>), ramp	42	17.40 ± 5.87	42	15.96 ± 6.14	.039
Balloon volume at first sensation (<i>mL</i>), step	42	6.21 ± 5.52	42	5.10 ± 4.78	.280
Balloon volume at pain (<i>mL</i>), step	42	21.67 ± 8.09	42	19.64 ± 11.06	.100
Mean pressure at pain (<i>mm Hg</i>), step	42	20.35 ± 6.44	42	16.87 ± 8.02	.006
Maximum pressure at pain (<i>mm Hg</i>), step	42	33.56 ± 10.17	42	28.36 ± 9.89	.002
Esophageal compliance	42	.98 ± .20	42	.92 ± .24	.129
Mean wall tension at pain	42	23.71 ± 10.03	42	17.66 ± 10.92	.002
Maximum wall tension at pain	42	38.13 ± 15.12	42	29.19 ± 13.76	.0004
VAS pain score, ramp	42	52.40 ± 20.60	42	47.21 ± 22.07	.045
Likert pain score, ramp	42	2.12 ± .63	42	1.98 ± .75	.184
VAS pain score, step	42	56.40 ± 26.04	42	54.40 ± 24.73	.452
Likert pain score, step	42	2.33 ± .82	42	2.24 ± .73	.382

abdominal discomfort, 86% had heartburn/acid reflux, distention was increased by 11% on tegaserod when

Comparing Omeprazole with Fluoxetine for Treatment of Patients with Heartburn and Normal Endoscopy who Failed Once Daily Proton Pump Inhibitors: Double-Blind Placebo-Controlled Trial



The Effect Of Melatonin In Functional Heartburn



3 - month, randomized, placebo-controlled trial

Hypnotherapy For Functional Heartburn

- Open label
- weekly session of hypnotherapy X7
- 9 FH patients aged 32 – 60 years
- There was a significant decrease in visceral anxiety ($p = 0.01$) and symptom severity ($p = 0.01$)
- All Patients reported improvement in symptoms (slight to substantial)

Proposed Treatment Guidelines for Reflux Hypersensitivity

- Proton pump inhibitors have a therapeutic value in reflux hypersensitivity regardless if it overlaps with GERD
- Neuromodulators, including tricyclic antidepressants and selective serotonin reuptake inhibitors can be used as primary therapy in reflux hypersensitivity or as add on therapy in reflux hypersensitivity that overlaps with proven GERD
- Acupuncture and hypnotherapy may have a role as sole treatment of reflux hypersensitivity, or in conjunction with another therapeutic modality.
- Anti-reflux surgery but not endoscopic GERD treatment modalities may have a therapeutic role in carefully selected reflux hypersensitivity patients.

“Reflux Hypersensitivity Is Not Contraindicated in Nissen Fundoplication”

- RH (N=28) vs NERD (N=126)
- Post surgery (3 months) - no difference
 - Total esophageal acid exposure
 - LES resting pressure
 - PPI consumption
 - Quality of life
- Symptoms resolution after 5 years – no difference

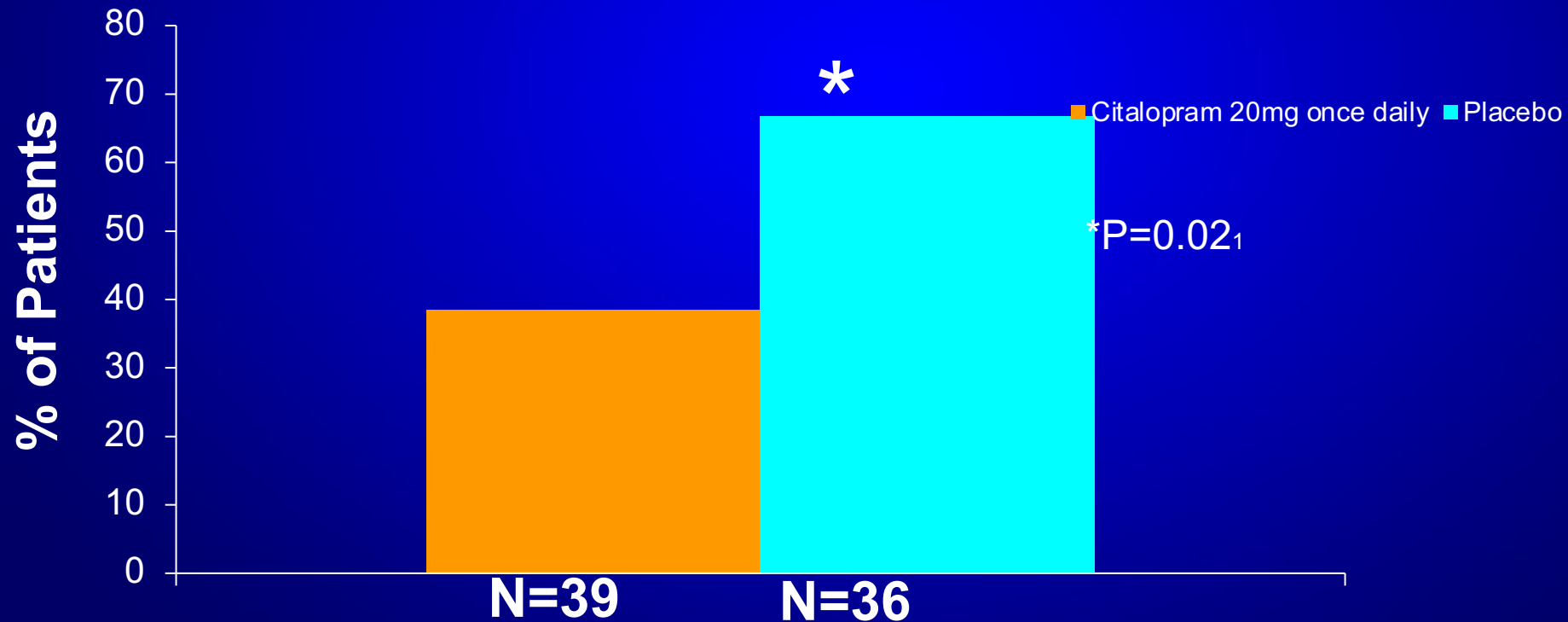
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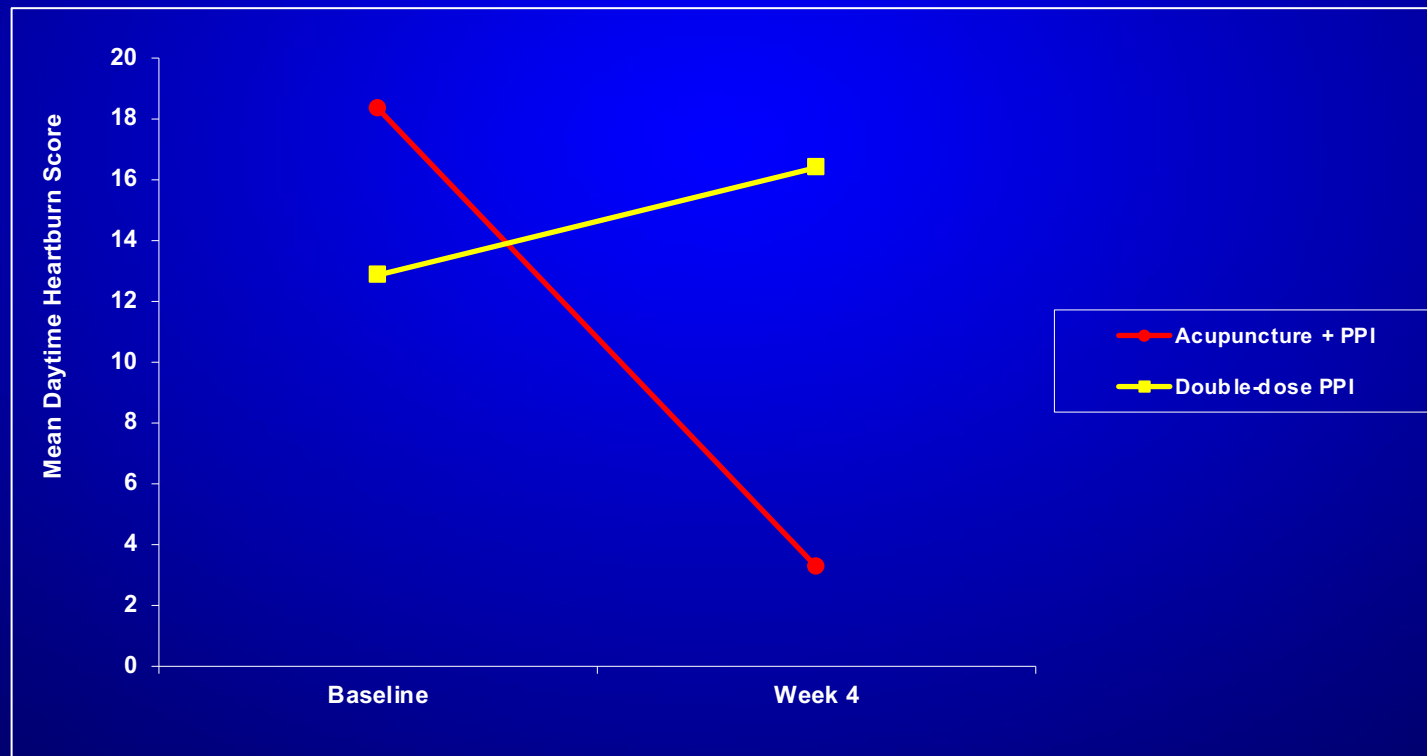
The Effect of Citalopram 20mg Once Daily Vs. Placebo in Patients with Reflux Hypersensitivity

- A randomized, double-blind, placebo-controlled trial for 6 months.
- % of patients who continued to report symptoms after full course of treatment



The Role of Acupuncture in Refractory Heartburn

For acupuncture + PPI – $P < 0.001$;
For double-dose PPI $P = \text{NS}$;
Between groups comparison – $P < 0.001$



The transcutaneous electrical stimulation system (TESS)

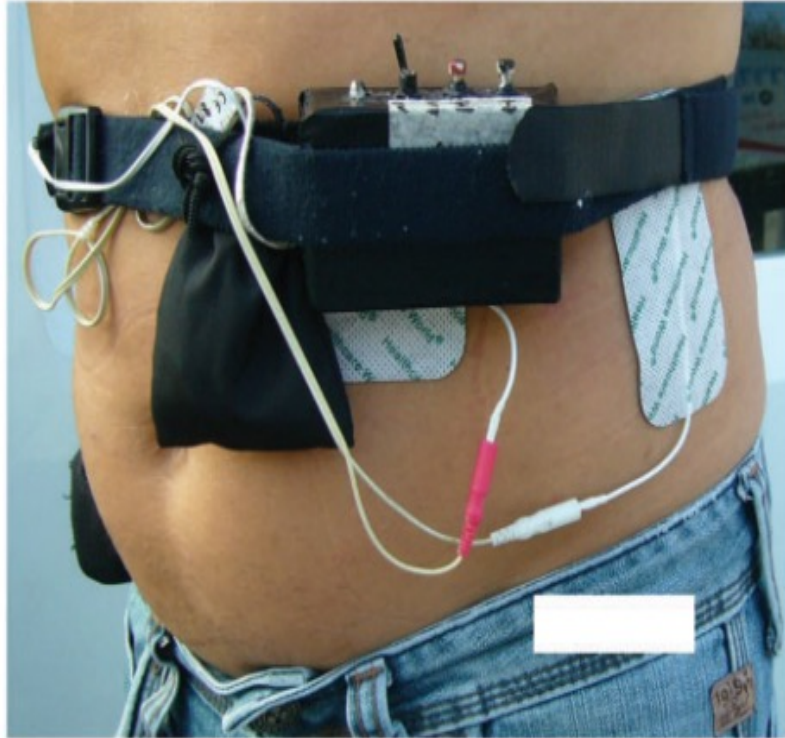


Figure 2. The transcutaneous electric stimulation device (TESS) is applied by a technician to the patient's abdominal wall and electrically stimulates the abdominal muscles

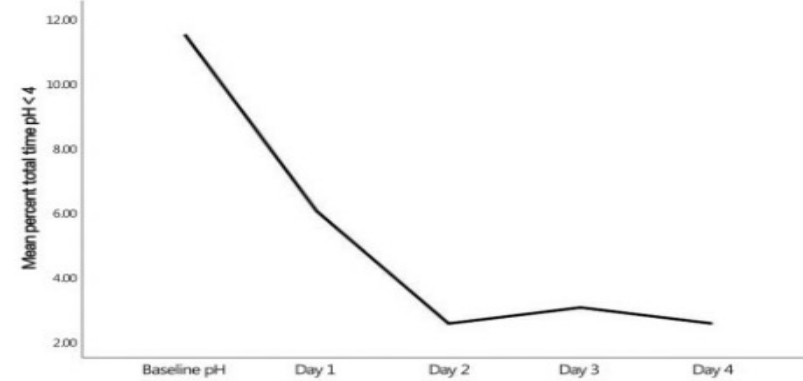
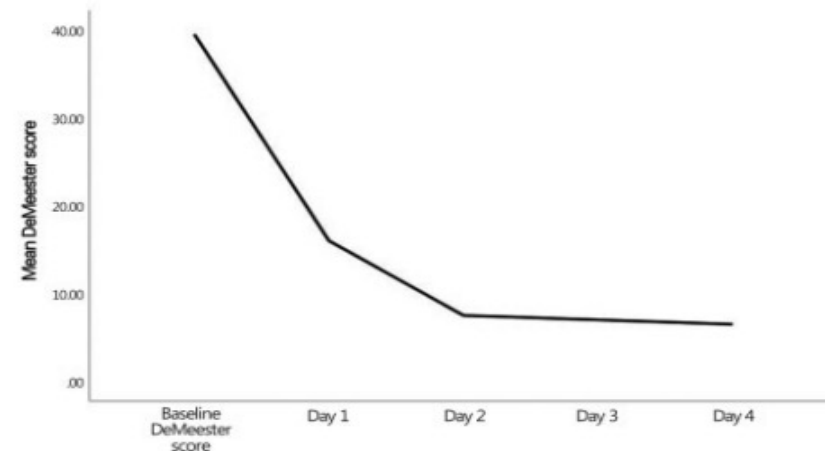


Figure 4. The decline curve of the mean percent total time pH < 4 from baseline to Day 4



Integrative Effects and Vagal Mechanisms of Transcutaneous Electrical Acustimulation on Gastroesophageal Motility in Patients With Gastroesophageal Reflux Disease

Bo Zhang, PhD^{1,2}, Yedong Hu, MD³, Xiaodan Shi, MD³, Wenna Li, RN³, Xin Zeng, MD³, Fei Liu, MD³, Jiande D.Z. Chen, PhD⁴ and Wei-Fen Xie, MD¹

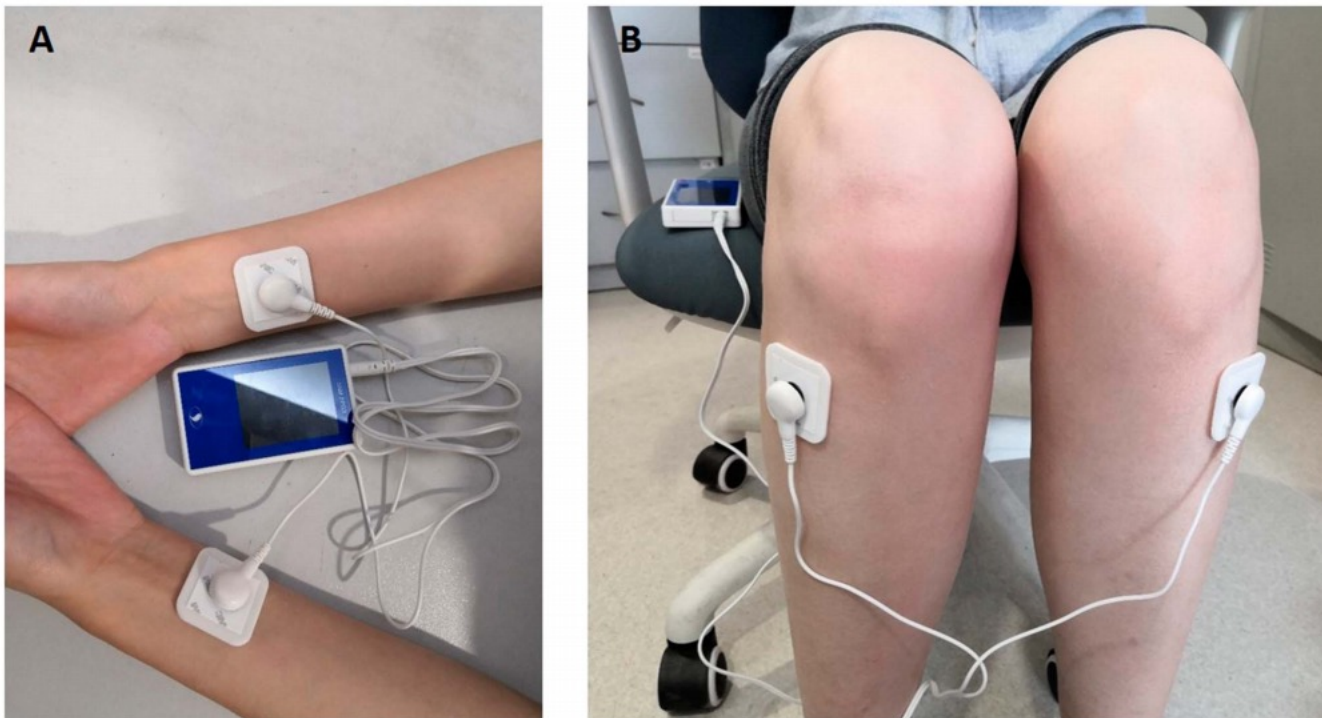


Figure 1. Transcutaneous electrical acustimulation in action. Two pairs of surface ECG electrodes were applied at bilateral PC6 (a) and ST36 (b), respectively. Two watch-size digital stimulators were used to deliver electrical stimulation.

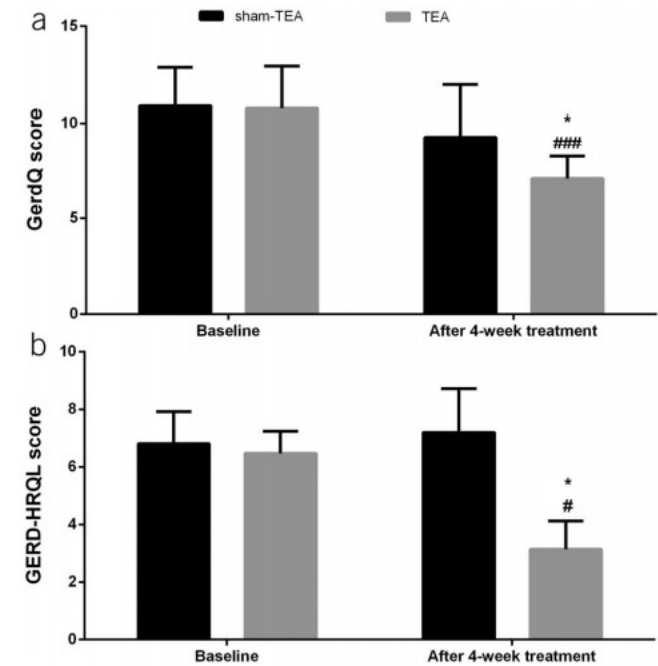
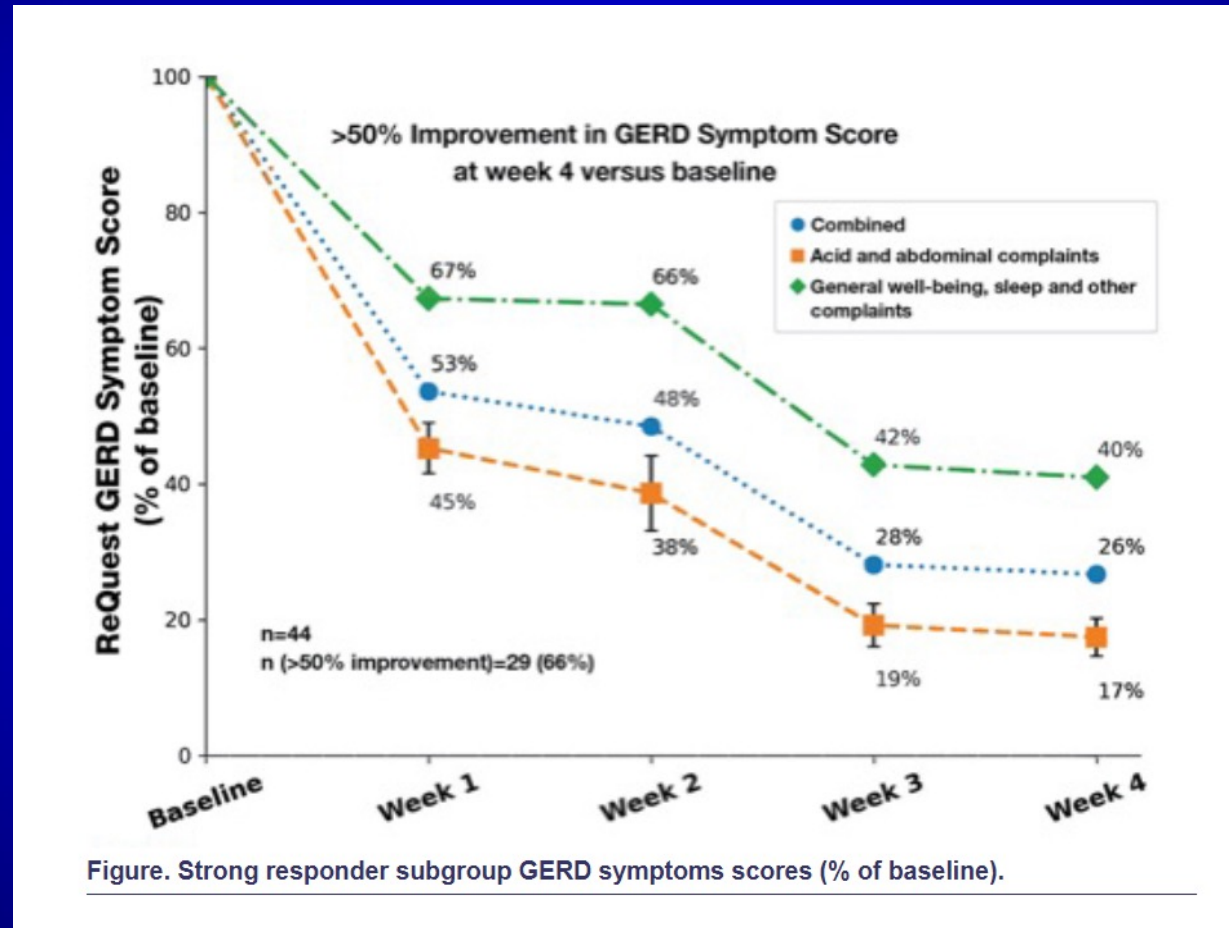


Figure 2. Effects of TEA on reflux-related symptoms and GERD-HRQL. TEA decreased GerdQ score (a) and GERD-HRQL score (b) (vs sham-TEA, $*P < 0.05$; vs baseline, $\#P < 0.05$; $###P < 0.001$). GERD, gastroesophageal reflux disease; TEA, transcutaneous electrical acustimulation; HRQL, health-related quality of life.

Four Weeks of a 1-g Daily of Maltosyl-Isomalto-Oligosaccharides, a Nondigestible, Nonabsorbable Prebiotic (ISOT-101, ISOThrive)



GERD dysbiosis is characterized by an overabundance of gram-negative bacteria

Thank You!



The MHMC Esophageal Research Group