Disclosures:

Speaker: Marcelo F. Vela, MD, MSCR, FACG
Consultant: Medtronic

Moderator: Afrin N. Kamal, MD
Dr. Kamal, faculty for this educational event, has no relevant financial relationship(s) with ineligible companies to disclose.

*All of the relevant financial relationships listed for these individuals have been mitigated.

OPIOID-INDUCED ESOPHAGEAL DYSFUNCTION: What to Know and How to Manage It

Marcelo F. Vela, MD, MSCR, FACG
Professor of Medicine
Director, Esophageal Disorders
Program Director, Esophageal Disorders Fellowship
Mayo Clinic, Scottsdale, AZ
OPIOID INDUCED ESOPHAGEAL DYSFUNCTION

- The opioid epidemic
- Effects of opioids in the GI tract and the esophagus
- Opioid-induced esophageal dysfunction (OIED)
  * Definition and clinical presentation
  * Manometric features
  * Pathophysiology
  * Evaluation and Management

THE OPIOID EPIDEMIC

- 11% of adults in the United States suffer from chronic pain
- Long-term opioids are prescribed to 3-4% of the US population
- More than 165,000 people have died in the US from opioid medication overdose 1999-2014
- 1.9 million people abusing or dependent on prescription opioids in 2013

Dowell et al. JAMA 2016
OPIOIDS: EFFECTS ON THE GI TRACT

- 3 peripheral opioid receptors in the enteric nervous system (µ, δ, κ) regulate various gastrointestinal functions

- Located in submucosal and myenteric plexus of the human stomach, small bowel, and colon

- Precise location of opioid receptors in the human esophagus has not been well characterized

Patel, Am J Gastroenterol 2019
Snyder and Vela, Curr Opin Gastroenterol 2020
OPIOIDS: EFFECTS ON THE GI TRACT

- Effects on the lower GI tract well described
  - Constipation

- Effects on stomach
  - Delayed gastric emptying
  - Increased pylorus tone

- Effects on duodenum
  - Increased tonic contractions
  - Decreased propulsive action

Patel, Am J Gastroenterol 2019

OPIOIDS: EFFECTS ON THE ESOPHAGUS

- Early studies with conventional manometry

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Methods</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Devulshahi et al. [20]</td>
<td>Experimental</td>
<td>10 Healthy adults given morphine sulfate</td>
<td>Decreased IES relaxation</td>
</tr>
<tr>
<td></td>
<td>Blinded</td>
<td>Morphine sulfate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>manometric</td>
<td>0.3 mg/kg body weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td>analysis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>5 Healthy adults given saline</td>
<td></td>
</tr>
<tr>
<td>Mindl et al. [21]</td>
<td>Experimental</td>
<td>10 Healthy adults given 8 mg morphine sulfate</td>
<td>Decreased IES pressure</td>
</tr>
<tr>
<td>Chassade et al. [16]</td>
<td>Experimental</td>
<td>10 Healthy adults given 2.5 mg/kg acetaminophen</td>
<td>Decreased IES relaxation</td>
</tr>
<tr>
<td>Penagini et al. [23]</td>
<td>Experimental</td>
<td>8 Healthy adults given morphine</td>
<td>Decreased IES relaxation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 μg/kg</td>
<td></td>
</tr>
<tr>
<td>Krishnaly et al. [22]</td>
<td>Retrospective</td>
<td>15 Patients taking chronic opioids</td>
<td>High amplitude contractions and incomplete IES relaxation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 with follow-up study off opioids</td>
<td>Normal IES relaxation for 3 patients examined after opioid cessation</td>
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Snyder and Vela, Curr Opin Gastroenterol 2020
OPIOIDS: EFFECTS ON THE ESOPHAGUS

- Early studies with conventional manometry

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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional manometry</td>
<td>Experimental</td>
<td>Blinded manometric analysis</td>
<td>10 Healthy adults given morphine sulfate, 0.3 mg/kg body weight</td>
</tr>
<tr>
<td>Donahue et al. [90]</td>
<td>1985</td>
<td></td>
<td>5 Healthy adults given saline</td>
</tr>
<tr>
<td>Mittal et al. [21]</td>
<td>Experimental</td>
<td>10 Healthy adults given 8 mg morphine sulfate</td>
<td>Decreased IES pressure</td>
</tr>
<tr>
<td>Chassade et al. [18]</td>
<td>Experimental</td>
<td>10 Healthy adults given 2.5 mg/kg acetaminophen</td>
<td>Decreased IES relaxation</td>
</tr>
<tr>
<td>Pavagadhi et al. [23]</td>
<td>Experimental</td>
<td>8 Healthy adults given morphine 100 mg/kg</td>
<td>Decreased IES relaxation</td>
</tr>
<tr>
<td>Kraichly et al. [29]</td>
<td>Retrospective</td>
<td>15 Patients taking chronic opioids 3 with follow-up ended off opioids</td>
<td>High-amplitude contractions and incomplete IES relaxation Normal IES relaxation for 3 patients examined after opioid cessation</td>
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</table>

These findings suggest that opioids impair inhibitory pathways in the esophagus

Snyder and Vela, Curr Opin Gastroenterol 2020

PHYSIOLOGY OF NORMAL ESOPHAGEAL MOTILITY

Goyal, J Clin Gastroenterol 2008
PHYSIOLOGY OF NORMAL ESOPHAGEAL MOTILITY

Goyal, J Clin Gastroenterol 2008

OPIOID-INDUCED ESOPHAGEAL DYSFUNCTION

Adapted from GI Motility online (May 2006) | doi:10.1038/gimo22
OPIOID-INDUCED ESOPHAGEAL DYSFUNCTION

Adapted from GI Motility online (May 2006) | doi:10.1038/gimo22

OIED: DEFINITION AND CLINICAL PRESENTATION

• **Definition:**
  - Symptoms of esophageal dysfunction
  - Documented chronic opioid use
  - Manometric abnormality consistent with OIED

  Snyder and Vela, Curr Opin Gastroenterol 2020

• **Symptoms:**
  - Dysphagia – 60%
  - Chest pain – 10%
  - “GERD” symptoms – 25%

  Snyder and Vela, Curr Opin Gastroenterol 2020
  Babaei, Neurogastroenterol Motil 2019
### OIED: RECENT STUDIES BASED ON HRM

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients Details</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>González et al. [32]</td>
<td>Prospective case series</td>
<td>5 Chronic opiate patients</td>
<td>2 Patients type III achalasia</td>
</tr>
<tr>
<td>Rotapsi et al. [26]</td>
<td>Retrospective</td>
<td>66 Patients on chronic opioids 55 patients on all opioids &gt; 24 h</td>
<td>Higher rate EGJOO, type II achalasia, DES and possibly jackhammer esophagus</td>
</tr>
<tr>
<td>Savillampi et al. [24]</td>
<td>Double-blind, randomized, crossover trial</td>
<td>14 Healthy volunteers, Naloxone or saline followed by remifentanil infusion at 1.2 and 3 mg/ml</td>
<td>Decreased swallow-evoked EGJ relaxation</td>
</tr>
<tr>
<td>Citreres et al. [33]</td>
<td>Cross-sectional</td>
<td>33 Opiate users 141 without opiate use</td>
<td>Higher RP, Higher DCI</td>
</tr>
<tr>
<td>Snyder et al. [27*]</td>
<td>Retrospective</td>
<td>225 Chronic opiate users on oxycodone, hydrocodone or tramadol</td>
<td>Achalasia in 24% of chronic opioid users</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effect of opioid type and 24 h morphine equivalent dose evaluated</td>
<td>Higher 24 h morphine equivalent dose in Achalasia (45 vs. 30 mg)</td>
</tr>
<tr>
<td>Rabiei et al. [31]</td>
<td>Retrospective</td>
<td>224 Opioid users and 1890 opioid-naive patients underwent HRM</td>
<td>Higher dysphagia prevalence in opioid group</td>
</tr>
<tr>
<td>Snyder et al. [28*]</td>
<td>Retrospective</td>
<td>72 Opium users, 100 nonopioin users, 24 healthy controls</td>
<td>Higher rate of impaired inhibition during multiple rapid swallows</td>
</tr>
</tbody>
</table>

**Achalasia type III**
- EGJ outflow obstruction
- Distal esophageal spasm
- Jackhammer esophagus

Snyder and Vela, Curr Opin Gastroenterol 2020
OIED: FINDINGS IN 121 OPIOID USERS

121 opioid users, 100 non-users
- Opioid users had higher rate of:

- Distal Esophageal Spasm
- EGJ Outflow Obstruction
- Achalasia type III
- Jackhammer Esophagus

Ratuapli, Am J Gastroenterol 2015

121 opioid users, 100 non-users
- These abnormalities more common with opioid use within 24 hours of study

Ratuapli, Am J Gastroenterol 2015
OIED: EFFECT OF OPIOID TYPE AND DOSE

Esophageal Manometry in 225 patients on opioids, 1,700 not on opioids:

HRM abnormalities consistent with OIED
- patients on opioids = 24% \( p = 0.0001 \)
- patients not on opioids = 9%
OIED: EFFECT OF OPIOID TYPE AND DOSE

Esophageal Manometry in 225 patients on opioids, 1,700 not on opioids:

- HRM abnormalities consistent with OIED
  - patients on opioids = 24%  \( p = 0.0001 \)
  - patients not on opioids = 9%

- HRM diagnosis in patients with OIED

Snyder, Am J Gastroenterol 2019

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OIED: EFFECT OF OPIOID TYPE AND DOSE

Esophageal Manometry in 225 patients on opioids:

**Percentage with OIED**

- Oxycodone: 31%
- Hydrocodone: 28%
- Tramadol: 12%

\( p = 0.0162 \)

Snyder, Am J Gastroenterol 2019
OIED: EFFECT OF OPIOID TYPE AND DOSE

Esophageal Manometry in 225 patients on opioids:

Percentage with OIED

- Oxycodone
- Hydrocodone
- Tramadol

OIED more common with oxycodone and hydrocodone compared to tramadol

p = 0.0162

Snyder, Am J Gastroenterol 2019

OIED: EFFECT OF OPIOID TYPE AND DOSE

24-hour opioid dosing in opioid users with versus without OIED

Snyder, Am J Gastroenterol 2019
OIED: EFFECT OF OPIOID TYPE AND DOSE

24-hour opioid dosing in opioid users with versus without OIED

Median 24-hour morphine equivalent dose:
OIED = 45 mg
No OIED = 30 mg

Dose effect:
Higher likelihood of OIED with stronger opioid doses

Snyder, Am J Gastroenterol 2019

OIED: EFFECT OF ACUTE CODEINE ADMINISTRATION

Geeraerts, Neurogastroenterol Motil 2020
OIED: EFFECT OF ACUTE CODEINE ADMINISTRATION

- 9 healthy volunteers
- All underwent HRM twice in random order after intragastric infusion of 60 mg codeine or placebo

EJG Relaxation

![Graph showing EJG Relaxation with Placebo and Codeine lines, with p = 0.0001]
OIED: EFFECT OF ACUTE CODEINE ADMINISTRATION

- 9 healthy volunteers
- All underwent HRM twice in random order after intragastric infusion of 60 mg codeine or placebo

**EJG Relaxation**

- Placebo
- Codeine

**Distal Latency**

- Placebo
- Codeine

*p = 0.0001

• 4/9 met criteria for EGJOO after codeine, none after placebo (*p = 0.0003*)

Geeraerts, Neurogastroenterol Motil 2020
OIED: EFFECT ON DEGLUTITIVE INHIBITION
Response to multiple rapid swallows

Snyder, Am J Gastroenterol 2020
OIED: EFFECT ON DEGLUTITIVE INHIBITION

Response to multiple rapid swallows

- Normal
- Impaired Inhibition

200 consecutive patients with esophageal symptoms
- 100 on opioids
- 100 not on opioids

20 healthy controls

All underwent manometry with multiple rapid swallows
OIED: EFFECT ON DEGLUTITIVE INHIBITION
Response to multiple rapid swallows

- 200 consecutive patients with esophageal symptoms
  - 100 on opioids
  - 100 not on opioids
- 20 healthy controls
- All underwent manometry with multiple rapid swallows

Incomplete MRS Inhibition

Snyder, Am J Gastroenterol 2020

Opioids appear to interfere with inhibitory signals in the esophagus
OIED: EVALUATION

• Diagnosis of OIED requires symptoms, opioid use, manometric abnormality on HRM
FUNCTIONAL LUMEN IMAGING PROBE (FLIP) TOPOGRAPHY

- 16 impedance planimetry sensors
- 1 pressure sensor
- Detects cross sectional area at each site

* Image courtesy of Dustin Carlson MD

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FUNCTIONAL LUMEN IMAGING PROBE (FLIP) TOPOGRAPHY

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- 1 pressure sensor
- Detects cross sectional area at each site

Normal FLIP Topography
- Repetitive antegrade contractions (RACs) = normal secondary peristalsis
- Normal EGJ distensibility index (DI)

NORMAL ESOPHAGEAL MOTILITY BY HRM AND FLIP TOPOGRAPHY

- Normal peristalsis
- Normal EGJ relaxation

- Repetitive antegrade contractions (RACs) = normal secondary peristalsis
- Normal EGJ distensibility index (DI)
Normal

Achalasia type III: reduced EGJ distensibility, repetitive retrograde contractions (RRCs)
FUNCTIONAL LUMEN IMAGING PROBE (FLIP) TO SCREEN FOR OIED

- Retrospective analysis of patients undergoing propofol-sedated EGD with FLIP topography for evaluation of esophageal symptoms
  - 17 chronic opioid users
  - 20 control patients not on opioids
- FLIP assessment
  - EGJ distensibility index
  - Evaluation of secondary peristalsis
- Opioid dose converted to 24-hour morphine equivalent

<table>
<thead>
<tr>
<th>FLIP Findings</th>
<th>Chronic Opioid Patients</th>
<th>Control Patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRCs</td>
<td>29%</td>
<td>0%</td>
<td>0.014</td>
</tr>
<tr>
<td>Mean DI</td>
<td>2.6</td>
<td>2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Abnormal DI</td>
<td>59%</td>
<td>55%</td>
<td>1</td>
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FUNCTIONAL LUMEN IMAGING PROBE (FLIP)
TO SCREEN FOR OIED

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- In opioid users:
  - RRCs more common (associated with DES, achalasia type III, EGJOO)
  - Significantly higher opioid dose in opioid users with low distensibility index (indicative of impaired EGJ relaxation)
  - FLIP topography performed during endoscopy for evaluation of esophageal symptoms may serve to screen for OIED

Snyder, DDW 2021
OIED: EVALUATION

• Diagnosis of OIED requires symptoms, opioid use, manometric abnormality on HRM

• These abnormalities may occur in the absence of opioid use - how to distinguish OIED from idiopathic motility disorder?
  - opioid cessation and repeat HRM is ideal, often not possible

• Amyl nitrate challenge during HRM may distinguish idiopathic from opioid-induced achalasia type III
  - re-bound LES contraction seen in idiopathic but not opioid-induced achalasia
  - effect on EGJOO, DES, Jackhammer esophagus not known

Babaei, Clin Gastroenterol Hepatol 2019
**OIED: MANAGEMENT RECOMMENDATIONS**

- Determine opioid use in all patients scheduled for HRM
  - Acute, short-term opioids: defer HRM until off medication
  - Chronic opioid user, no plans to discontinue: perform HRM on opioids

- No clinical trials evaluation management strategies for OIED

- Current options are based on expert opinion and limited available data:
  - Opioid cessation (through formal cessation clinic)
  - Change dose or opioid type?
  - Opioid antagonists have not been studied
  - May treat with same strategies as idiopathic achalasia, DES, EGJOO, Jackhammer

**OIED: SUMMARY**

- Opioid use is extremely common

- Opioids appear to interfere with esophageal inhibitory pathways, leading to impaired EGJ relaxation and vigorous/spastic contractions, manifested by motility abnormalities diagnosed by HRM:
  - Achalasia type III, Distal Esophageal Spasm, EGJ outflow obstruction, Jackhammer esophagus

- OIED diagnosis: esophageal symptoms + chronic opioid use + HRM abnormality
  - Amyl nitrate challenge may distinguish idiopathic from opioid-induced achalasia
  - Abnormal FLIP topography may serve as a screening tool
OIED: SUMMARY

- Document opioid use in all patients undergoing HRM

- There are no clinical trials to guide management, options include:
  - Opioid cessation
  - Change in opioid dose or type
  - Opioid antagonists?
  - Treat as idiopathic motility disorder

Thank you
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ACG Women in GI Circle

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