UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: lowrymf@upmc.edu

TODAY'S TOPIC:

Requested Topic: Opioid-Induced Constipation Evidence Spotlight

Background:

Guidelines recommend use of peripherally acting mu-opioid receptor antagonists (PAMORAs) for OIC and have less strong recommendations for intestinal secretagogues, such as lubiprostone, although lubiprostone is FDA-approved for OIC.

Importance:

OIC is common in our palliative care population. It is important for palliative care clinicians to be aware of the *evidence* for treating OIC.

The Literature:

Clin Gastroenterol Hepatol. 2018 Oct; 16(10):1569-1584.

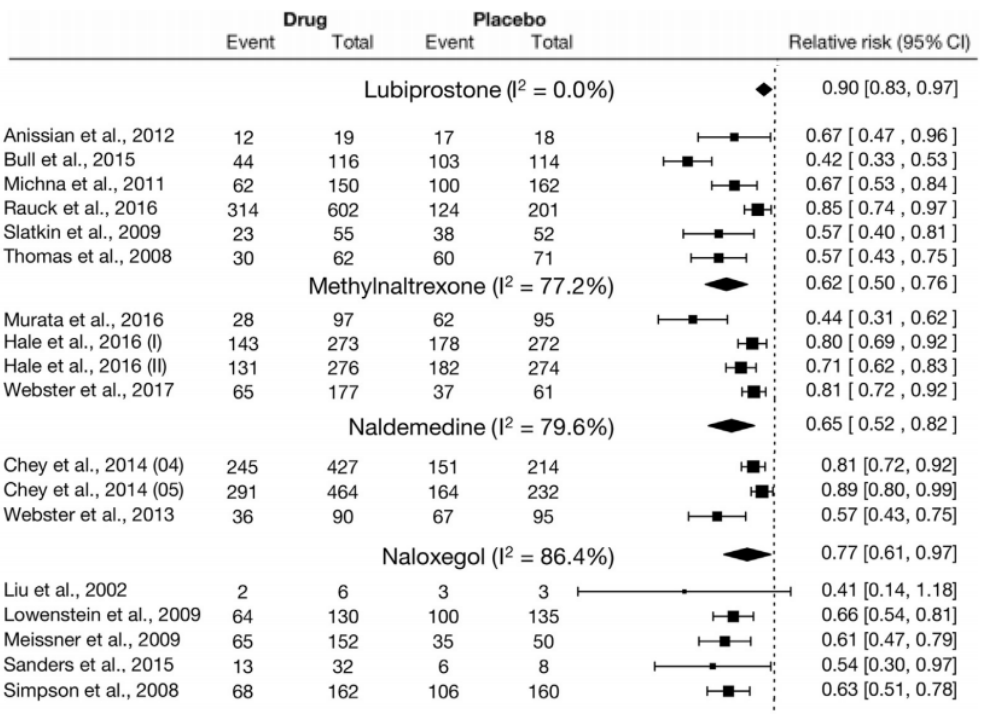
Efficacy of Treatments for Opioid-Induced Constipation: Systematic Review and Meta-analysis

Methods:

- Systematic review through March 2017
- Relative risk defined as risk of failure to respond to treatment of medication
- OIC definitions varied between studies, heterogeneity existed across studies
- Outcomes: Most common primary outcome was 3 or more complete spontaneous bowel movements/week over the trial period

Results: 27 RCTs (*23 trials PAMORAs*, 3 trails lubiprostone)

- All agents FDA-approved for OIC: combined RR 0.70 [0.64-0.75]; NNT 5
- Lubiprostone (Amitiza): Chronic nonmalignant pain
  - Number needed to treat (NNT): 15
- Methylnaltrexone (Relistor): Orthopedic procedure, chronic nonmalignant pain, advanced illness, methadone maintenance program
  - NNT: 3.4
- Naldemedine (Symproic): Chronic nonmalignant pain
  - NNT: 5
- Naloxegol (Movantik): Chronic Nonmalignant pain
  - NNT: 7



	Drug Event	Drug Total	Placebo Event	Placebo Total	Relative risk (95% CI)
Lubiprostone (I^2 = 0.0%)					0.90 [0.83, 0.97]
Anissian et al., 2012	12	19	17	18	0.67 [0.47 , 0.96]
Bull et al., 2015	44	116	103	114	0.42 [0.33 , 0.53]
Michna et al., 2011	62	150	100	162	0.67 [0.53 , 0.84]
Rauck et al., 2016	314	602	124	201	0.85 [0.74 , 0.97]
Slatkin et al., 2009	23	55	38	52	0.57 [0.40 , 0.81]
Thomas et al., 2008	30	62	60	71	0.57 [0.43 , 0.75]
Methylnaltrexone (I^2 = 77.2%)					0.62 [0.50 , 0.76]
Murata et al., 2016	28	97	62	95	0.44 [0.31 , 0.62]
Hale et al., 2016 (I)	143	273	178	272	0.80 [0.69 , 0.92]
Hale et al., 2016 (II)	131	276	182	274	0.71 [0.62 , 0.83]
Webster et al., 2017	65	177	37	61	0.81 [0.72 , 0.92]
Naldemedine (I^2 = 79.6%)					0.65 [0.52 , 0.82]
Chey et al., 2014 (04)	245	427	151	214	0.81 [0.72, 0.92]
Chey et al., 2014 (05)	291	464	164	232	0.89 [0.80, 0.99]
Webster et al., 2013	36	90	67	95	0.57 [0.43, 0.75]
Naloxegol (I^2 = 86.4%)					0.77 [0.61, 0.97]
Liu et al., 2002	2	6	3	3	0.41 [0.14, 1.18]
Lowenstein et al., 2009	64	130	100	135	0.66 [0.54, 0.81]
Meissner et al., 2009	65	152	35	50	0.61 [0.47, 0.79]
Sanders et al., 2015	13	32	6	8	0.54 [0.30, 0.97]
Simpson et al., 2008	68	162	106	160	0.63 [0.51, 0.78]

- Other notable findings:
  - Mean dose of opioids at baseline was a significant predictor of trial outcome
    - Higher doses associated with lower RR (better outcome for OIC agent)
  - Populations refractory to laxatives responded better to OIC agent
- Safety:
  - Common adverse effects were: diarrhea, abdominal pain, or nausea/vomiting

Conclusion

- PAMORAs are safe and effective for treatment of OIC

How does this affect QOL? See below for a *very* brief summary on QOL …

Clin J Pain. 2020 Sep;36(9):716-722.

Opioid-induced Constipation: A Review of Health-related Quality of Life, Patient Burden, Practical Clinical Considerations, and the Impact of Peripherally Acting Mu-Opioid Receptor Antagonists

Objective: To provide an overview of OIC and its influence on disease burden and quality of Life (QOL)

Outcomes: Different quality of life assessment tools utilized in separate studies

Methods: Narrative review

Results:

- All 3 PAMORAs FDA-approved for OIC improve QOL on patient-reported QOL scales

Conclusion:

- If OIC is treated, QOL improves… which is not totally groundbreaking

Bottom Line:

- UPMC has a formulary for OIC: **UPMC Formulary**: OIC 2019
  - Preferred, formulary agent: 1st line: Naloxegol (Movantik®)
    - Formulary-restricted agents (restricted to: Pain Service, Oncology, Critical Care, GI, Palliative Care): 2nd line: Naldemedine (Symproic®) 3rd line: Methylnaltrexone (Relistor®)
- Methylnaltrexone is technically the only agent approved for OIC that has been studied in a population other than chronic nonmalignant pain, including an advanced illness population
- It is possible that patients on higher Oral Morphine Equivalents (OMEs) have better response to OIC agents than those on lower OMEs
- It is possible that patients with laxative-refractory OIC have better response to OIC agents than those patients without laxative-refractory OIC
- Because of the two points above… it is possible that patients with more severe OIC will respond better to OIC agents
- When considering NNT, must also consider quality of evidence… NNT may not give the whole picture, must dig further into what types of studies helped formulate this number…
- It is unclear if PRN usage of these agents is as effective as scheduled use given the responses of these trials were defined as spontaneous bowel movements *per week*, not Yes/No response after dose administered…

CLINICAL PEARL: PAMORAs are safe and effective for opioid induced constipation