2014: ACG-FDA Public Forum

American College of Gastroenterology
&
U.S. Food and Drug Administration

Toward Improving the Quality of Colonoscopy: Evidenced-Based State of the Art in Bowel Preparation

Sponsored by the ACG FDA Related Matters Committee

Agenda & Speakers

Moderators:

Lawrence Cohen, MD, FACG Robert Fiorentino, MD (FDA)

Topics:

The FDA perspective on bowel preparation registration trials (Robert Fiorentino, MD)

What is the evidence for an optimal dosing scheme and bowel preparation formulation? (Paul Moayyedi, MD)

What are the immediate and delayed safety issues surrounding over the counter and prescription bowel preparations? (Philip Schoenfeld, MD)

What are the optimal endpoints for assessing bowel preparation in clinical practice or trials? (Douglas Rex, MD)

Open Forum Discussion

ACG 2014 Bowel Prep Workshop
FDA Perspective

Robert P. Fiorentino, M.D., M.P.H.
FDA, Division of Gastroenterology & Inborn Errors
October 2014

Outline

- Case Studies: Safety
  - Visicol / Osmoprep (phosphate nephropathy)
  - HalfLytely (ischemic colitis)
- General Efficacy Remarks
  - Shared Goals
  - Endpoint Selection
  - Noninferiority design considerations
  - Choice of Regimen
    - *(day before, same day or split dose?)*
  - "Combination Rule"

FDA Approved Bowel Cleansing Products

Oral Sodium Phosphate Preps
- Visicol (2000)
- OsmoPrep (2006)

Polyethylene Glycol Preps
- GoLYTELY (4L) (1984)
- Colyte (4L) (1984)
- OCL Solution(4L) (1986)
- NuLYTELY(4L) (1991)
- MoviPrep (2L) (2006)

Sulfate Salt Preps
- SUPREP (2010)

Others (Combinations)
- HalfLytely (2004, 2007, 2010)
- Prepopik (2012)
- Suclear (2013)

Case Study: Sodium Phosphate Preps

- In September 2003, Desmeules et al published a case report of acute phosphate nephropathy followed by persistent renal insufficiency in a 71-year old woman who took 90 mL of an OSP solution as a cathartic.
- In November 2005, Markowitz et al published a case series study describing 21 **biopsy-proven** cases of acute phosphate nephropathy in patients who took OSP and had no history of hypercalcemia or superimposed renal pathology.
  - 18 patients were diagnosed with acute renal failure within 2 months of colonoscopy, and all were diagnosed within 5 months.
- FDA review of the above literature and the FDA Adverse Event Reporting System (AERS) revealed 10 additional unique cases of renal failure associated with use of OSP solution and 10 cases of renal failure associated with use of OSP tablets.

Case Study: Sodium Phosphate Preps

- In 2006, FDA took steps to include information regarding the risk of acute phosphate nephropathy associated with the use of OSP products for bowel cleansing to the WARNINGS section of the existing prescription labeling for Visicol, as well as OsmoPrep.
- In 2006, the Agency issued an FDA Alert on OSP products for bowel cleansing (2006 FDA Alert), which included information for healthcare professionals and patients, and a science background paper *(links provided below).*

For more information:

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126084.htm
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161581.htm

Case Study: Sodium Phosphate Preps

- In 2008, FDA conducted a new analysis of the AERS reports involving OSP-associated acute phosphate nephropathy, as well as a review of the recent medical literature
  - Between 2006 to 2008 there were 20 reported cases of kidney injury associated with the use of OsmoPrep, 3 were biopsy-proven cases of acute phosphate nephropathy.
  - The onset of kidney injury in these cases varied, occurring in some within several hours of use of these products and in other cases up to 21 days after use.
- This review demonstrated that acute phosphate nephropathy could lead to serious kidney injury, requiring dialysis or kidney transplant, and in rare instances, death.
- FDA determined that, “taking steps to ensure that healthcare providers and their patients are better informed about the risk of OSP-associated acute phosphate nephropathy might help to decrease the number of these adverse events.”

Case Study: Sodium Phosphate Preps

- **This information resulted in:**
  - A determination that OSP oral solution for *bowel cleansing* are prescription products and not available over the counter *(laxatives still OTC)*
  - A Boxed Warning within the Osmoprep and Visicol labels
  - The Development of and distribution of a Medication Guide and a Communication Plan
  - Postmarketing clinical trials needed to evaluate safety
    - *Randomized, controlled clinical trial evaluating the risk of developing acute kidney injury, comparing patients undergoing bowel cleansing using prescription OSP products to patients undergoing bowel cleansing using PEG-containing products.*

Case Study: HalfLytely

- HalfLytely/Bisacodyl Bowel Prep Kit was originally developed to reduce the prep volume (2L) compared to standard bowel preparations (4L)
- HalfLytely was approved in 2004 with a bisacodyl dose of 20 mg.
- Following this approval, several reports of ischemic colitis were received.
- In May 2006, HalfLytely labeling was revised to include reports of ischemic colitis (IC)
- IC reports were suspected to be related to the dose of bisacodyl (20 mg) included in the original kit.
- The dose of bisacodyl was reduced from 20 mg to 10 mg in 2007. Data demonstrated similar efficacy between HalfLytely with 20 mg bisacodyl and HalfLytely with 10 mg bisacodyl.

http://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm223057.pdf

Case Study: HalfLytely

- Although the risk of ischemic colitis is low (about 1 in 100,000 for the HalfLytely and bisacodyl 20mg prep) it appeared to be reduced by the dose reduction to 10 mg based on post-market reporting.
- In the approval letter for the HalfLytely and Bisacodyl (10 mg) Bowel Prep Kit the FDA requested that additional studies be performed to evaluate lower doses of bisacodyl.
- A trial compared HalfLytely with 5 mg of bisacodyl to the approved HalfLytely with 10 mg of bisacodyl.
- After the marketing of the HalfLytely and Bisacodyl (10 mg) Bowel Prep Kit , 3 cases of ischemic colitis were reported.
- Ultimately, the dose of Bisacodyl in the Bowel Prep Kit was reduced to 5mg.

http://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm223057.pdf

Communicating Safety

- Oral sodium phosphate products for colon cleansing now have boxed warnings
- Prescription bowel prep labels contain similar *Warnings & Precautions*
  - **Serious Fluid and Serum Chemistry Abnormalities**
  - **Cardiac Arrhythmias**
  - **Seizures**
  - **Use in Patients with Renal Impairment**
  - **Ischemic Colitis**

More Recent Trials…

- Assess renal and hemodynamic safety
  - Orthostatic BP measurements on the day of colonoscopy
  - More distal renal function assessment timepoints post colonoscopy
- Assess risk factors for renal injury
  - Antihypertensive drugs / discontinuation
  - IV fluids other therapies peri-colonoscopy

Efficacy: Consider Our Goals

- ✓ Excellent visualization of the mucosa
- ✓ Adequate visualization of all segments (e.g., ascending colon)
- ✓ Appropriate timing of administration prior to endoscopy
- ✓ Ease for patient (i.e., completion of prep)

Efficacy Considerations

- There isn't a universally accepted endpoint model to assess efficacy. ***Why not?***
  - Trial proposals reviewed on a case-by-case basis
  - Typically see multiple outcome scales and definitions of study success for each prep
  - Various approaches used to evaluate colonic segments (e.g., ascending colon)
  - Evaluation of bowel preps could benefit from a standardized approach

Efficacy Considerations

- Non-inferiority *"creep"*
  - Important to maintain efficacy of products over time, especially if goal is to have the *"lowest volume prep"*
- Various clinical programs evaluating day before colonoscopy, day of colonoscopy or split dose regimens, *and various combos*
  - Recent split dose regimens have been labeled as the *Preferred Regimen*

"Combination Rule"

- Various combination of osmotic agents (PEG, salts) with or without laxatives are possible, each having a contribution to the bowel cleansing
- Regulations (21 CFR 300.50) require that:

Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

"Combination Rule"

- E.g., the combination should be better than the components alone
- How do you demonstrate that each component of a bowel prep makes a contribution to the claimed effect?
- Burden of proof rests with the sponsor
- *Imagine all the combinations possible…*

Wrap Up

- We need to be vigilant to the safety of preps given the history of these products
- Common goal: maximize the rate of excellent preps (positive public health impact)
- Maintain excellence across new products and dosing regimens
- Don’t sacrifice these for convenience only
- Plenty of opportunity for standardization of endpoints and trial designs

Thank You!

What is the evidence for an optimal dosing scheme and bowel preparation formulation?

Paul Moayyedi
Co-Editor in Chief of American Journal of Gastroenterology
Director, Division of Gastroenterology
Richard Hunt/AstraZeneca Chair
McMaster University, Hamilton Ontario, Canada

FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University
THE COCHRANE COLLABORATION®

Disclosures

- No relevant financial declaration

Introduction

- Type of bowel preparation
  - 4 liter PEG
  - 2 liter PEG
  - Sodium picosulfate
  - Oral sulfate solutions
- Previous day versus split dose
- Same day versus split dose
- How GRADE assessment can guide future RCTs

Information evaluated

- Previous systematic reviews of RCTs
- RCTs identified by Medline search
- Meta-analyses

Optimizing Adequacy of Bowel Cleansing for Colonoscopy: Recommendations From the US Multi-Society Task Force on Colorectal Cancer

David A. Johnson[1], Alan N. Barkun[2], Larry B. Cohen[3], Jason A. Dominitz[4], Tonya Kaltenbach[5], Myriam Martel[2], Douglas J. Robertson[6,7], C. Richard Boland[8], Frances M. Ciarleglio[9], David A. Lieberman[10], Theodore R. Levin[11] and Douglas K. Rex[12]

Am J Gastroenterol 2014; 109:1528–1545; doi:10.1038/ajg.2014.272; published online 16 September 2014

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States (1). Colonoscopy can prevent CRC by the detection and removal of precancerous lesions. In addition to CRC screening and surveillance, colonoscopy is used widely for the diagnostic evaluation of symptoms and other positive CRC screening tests. Regardless of indication, the success of colonoscopy is linked closely to the adequacy of preprocedure bowel cleansing.

Unfortunately, up to 20–25% of all colonoscopies are reported to have an inadequate bowel preparation (2,3). The reasons for this range from patient-related variables such as compliance with preparation instructions and a variety of medical conditions that make bowel cleansing more difficult to unit-specific factors (eg, extended wait times after scheduling of colonoscopy) (4). Adverse consequences of ineffective bowel preparation include lower adenoma detection rates, longer procedural time, lower cecal intubation rates, increased electrocautery risk, and shorter intervals between examinations (3,5–7).

Bowel preparation formulations intended for precolonoscopy cleansing are assessed based on their efficacy, safety, and tolerability. Lack of specific organ toxicity is considered to be a prerequisite for bowel preparations. Between cleansing efficacy and tolerability, however, the consequences of inadequate cleansing suggest that efficacy should be a higher priority than tolerability. Consequently, the choice of a bowel cleansing regimen should be based on cleansing efficacy first and patient tolerability second. However, efficacy and tolerability are closely interrelated. For example, a cleansing agent that is poorly tolerated and thus not fully ingested may not achieve an adequate cleansing.

The goals of this consensus document are to provide expert, evidence-based recommendations for clinicians to optimize colonoscopy preparation quality and patient safety. Recommendations are provided using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) scoring system, which weighs the strength of the recommendation and the quality of the evidence (8).

METHODS

Search Strategy

Computerized medical literature searches were conducted from January 1980 (first year of approval of polyethylene glycol–electrolyte lavage solution [PEG-ELS]–based preparation by the Food and Drug Administration [FDA]) up to August 2013 using MEDLINE, PubMed EMBASE, Scopus, CENTRAL, and ISI Web of knowledge. We used a highly sensitive search strategy to identify reports of randomized controlled trials (9) with a combination of medical subject headings adapted to each database and text words related to colonoscopy and gastrointestinal agents, bowel preparation, generic name, and brand name. The complete search terms are available in **Appendix A.** Recursive searches and cross-referencing also were performed using a "similar articles" function; hand searches of articles were identified after an initial search. We included all fully published adult human studies in English or French.

A systematic review of published articles and abstracts presented at national meetings was performed to collect and select the evidence. A meta-analysis and consensus agreement were used to analyze the evidence. Expert consensus was used to formulate the recommendations. The GRADE system was used to rate the strength of the recommendations. The guideline was reviewed by committees of and approved by the governing boards of the member societies of the Multi-Society Task Force on Colorectal Cancer (American College of Gastroenterology, American Gastroenterological Association, and American Society of Gastrointestinal Endoscopy).

[1]Eastern VA Medical School, Norfolk, Virginia, USA; [2]McGill University Health Center, McGill University, Montreal, Canada; [3]Icahn School of Medicine at Mount Sinai, New York, New York, USA; [4]VA Puget Sound Health Care System and University of Washington, Seattle, Washington, USA; [5]Veterans Affairs Palo Alto, Stanford University School of Medicine, Palo Alto, California; [6]VA Medical Center, USA; [7]Geisel School of Medicine at Dartmouth, White River Junction, Vermont, USA; [8]Baylor University Medical Center, Dallas, Texas, USA; [9]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [10]Oregon Health and Science University, Portland, Oregon, USA; [11]Kaiser Permanente Medical Center, Walnut Creek, California, USA; [12]Indiana University School of Medicine, Indianapolis, Indiana, USA. **Correspondence:** David A. Johnson, Eastern VA Medical School, Norfolk, Virginia, USA. E-mail: dajevms@aol.com

FARNCOMBE
Farncombe Family Digestive Health Research Institute

Johnson DA et al. AJG 2014; 109: 1528-45

McMaster University
THE COCHRANE COLLABORATION®

4 liter versus 2 liter PEG

- High volume (≥ 3 l) vs. low volume (< 3 l)
- 28 trials
- 7208 ITT patients
- No difference in bowel cleanliness
- OR = 1.03 (95% CI = 0.80 to 1.32)

Johnson DA et al. AJG 2014; 109: 1528-45

PEG versus sodium picosulfate

- Sodium picosulfate versus PEG solutions
- 11 trials
- 3097 ITT patients
- No difference in bowel cleansing
- OR = 0.92 (95% CI = 0.63 to 1.36)

Johnson DA et al. AJG 2014; 109: 1528-45

Oral sulfate solution versus PEG

- Oral sulfate solutions versus PEG
- 2 trials (different PEG regimens)
- 923 ITT patients
- No difference
- OR = 1.12 (95% CI = 0.77 to 1.62)

Johnson DA et al. AJG 2014; 109: 1528-45

Split dose versus day before

- PEG solutions
  - 8 trials, 1990 ITT patients
  - Split improved cleanliness
  - OR = 4.38; 95% CI = 1.88 to 10.21
- Sodium picolsulfate
  - One trial, 250 ITT patients
  - Split dose improved cleanliness
  - OR 3.54; 95% CI = 1.95 to 6.45

Split dose versus same day

- No RCTs
- One RCT same day 4 l PEG versus day before
- 136 patients
- Same day superior
- OR = 2.63 (1.31 to 5.27)

Varughese S et al. AJG 2010; 105: 2368-74

Summary of what the evidence tells us

- Can be reasonably confident
  - 4 l PEG, 2 l PEG, sodium picosulfate similar efficacy
  - Split dose better than previous day preparations (PEG)
- Need more data to be confident
  - Oral sulfate solution
  - Same day preparations for afternoon colonoscopy

Evidence Based Medicine

FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

Gordon Guyatt

"Evidence based Medicine" ACP Journal Club 1991

FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

- Grades the quality of evidence
- Gives a strength of recommendation
- Systematic transparent approach
- Developed by a Working Group since 2000
- Endorsed by over 90 organizations worldwide

FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University
THE COCHRANE COLLABORATION®

60+ Organizations

2005 2006 2007 2008 2009 2010 2011

FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

Quality of the evidence

- High
  - further research unlikely to change effect estimate
- Moderate
  - more research likely to change effect estimate
- Low
  - more research very likely to change effect estimate
- Very low
  - Any effect estimate very uncertain

Strength of recommendation

- Strong recommendation
  - Applies to most patients most of the time
- Weak recommendation
  - Applies only to some patients

FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

FDA-APPROVED PREPARATIONS

Recommendations

1. Selection of a bowel-cleansing regimen should take into consideration the patient's medical history, medications, and, when available, the adequacy of bowel preparation reported from prior colonoscopies (***Strong recommendation, moderate-quality evidence***).
2. A split-dose regimen of 4l PEG-ELS provides high-quality bowel cleansing (***Strong recommendation, high-quality evidence***).
3. In healthy nonconstipated individuals, a 4-L PEG-ELS formulation produces a bowel-cleansing quality that is not superior to a lower-volume PEG formulation (***Strong recommendation, high-quality evidence***).

Johnson DA et al. AJG 2014; 109: 1528-45

Confidence assessment criteria (quality of the evidence)

Study Design	Confidence in estimates	Lower if	Higher if
Randomised trial →	High	Risk of bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study →	Low		
	Very low		

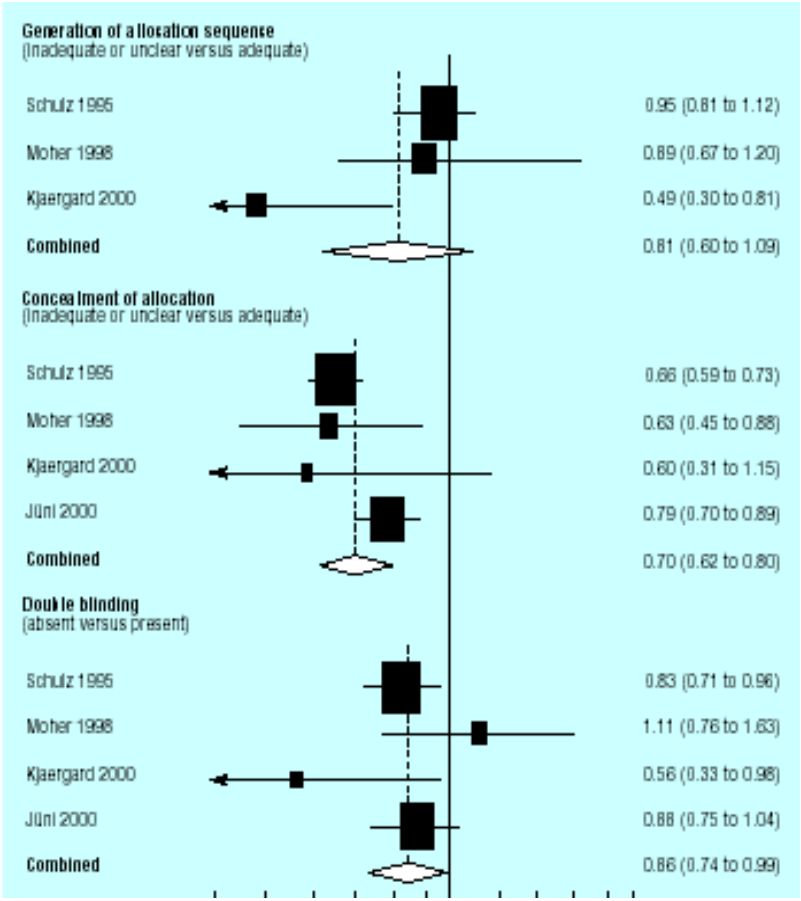
FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

Individual quality criteria

- Method of randomization
- Concealment of allocation
- Masking



Juni P et al. BMJ 2001; 323: 42-6

FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

Confidence in 2L vs 4L PEG data

- 24 trials for 2L vs 4L
- In ALL trials patients were not blinded
- Not the fault of the investigators
- Patients should be unblinded to assess tolerance
- Nevertheless ALL trials are at high risk of bias

Quality of 2L vs 4L data

- Only 6/24 (25%) met minimal standards for randomization and concealment of allocation
- 0/24 met highest standards for randomization and concealment of allocation

Confidence assessment criteria (quality of the evidence)

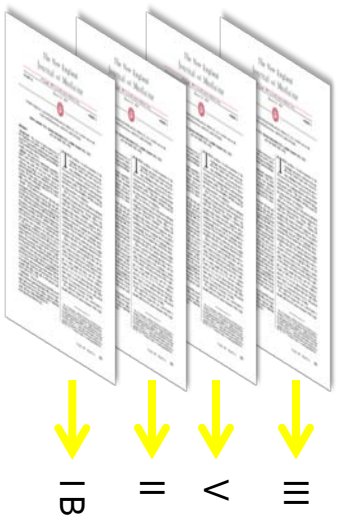
Study Design	Confidence in estimates	Lower if	Higher if
Randomised trial →	High	Risk of bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study →	Low		
	Very low		

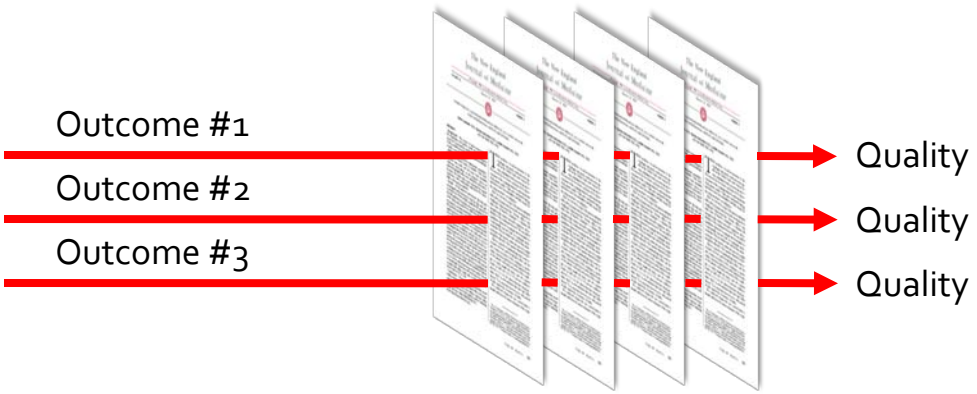
FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

A grading system needs to be outcome-centric





Old system

GRADE

Formulate question

Select outcomes

Rate importance

Outcomes across studies

Create evidence profile with GRADEpro

Rate quality of evidence for each outcome

P
I
C
O

Outcome Critical

Outcome Critical

Outcome Important

Outcome Less important

High
Moderate
Low
Very low

Summary of findings & estimate of effect for each outcome

RCT start high, obs. data start low

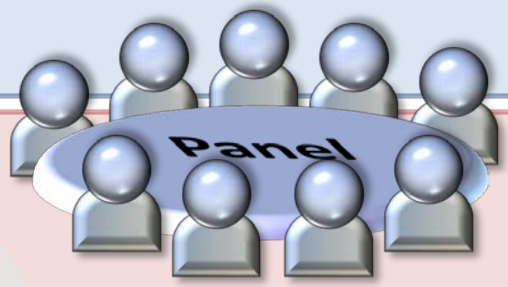
Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

Systematic review



Guideline development

:

- For or against (direction)
- Strong or weak (strength)

By considering:

- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences

Revise if necessary by considering:

- ❑ Resource use (cost)


AMERICAN GASTROENTEROLOGICAL ASSOCIATION

Colorectal Cancer Screening and Surveillance: Clinical Guidelines and Rationale—Update Based on New Evidence

Rate
overall quality of evidence
across outcomes based on lowest quality
of ***critical*** outcomes

- "We recommend using…"
- "We suggest using…"
- "We recommend against using…"
- "We suggest against using…"

FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION

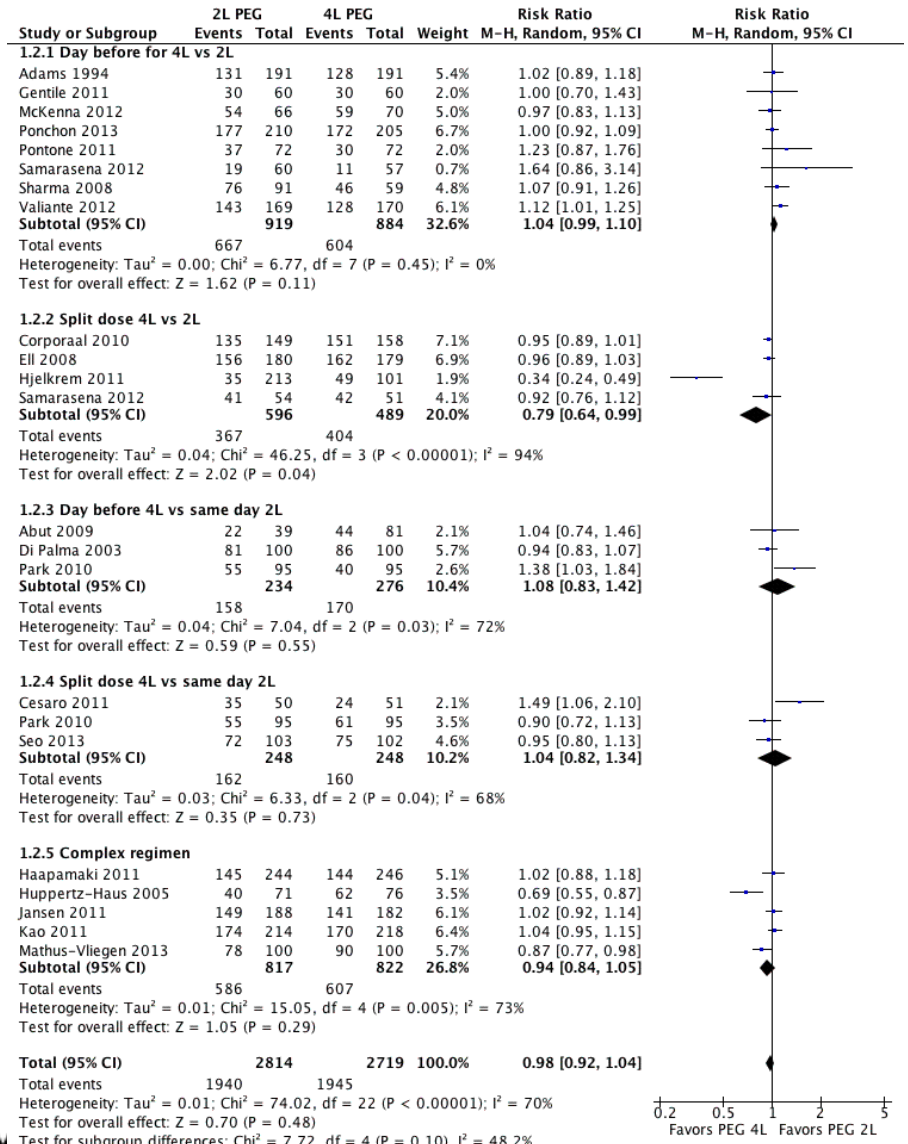
Patient perspective critical

- Clinician perspective
  - Bowel cleanliness
- Patient perspective
  - Reduce cancer risk > high risk ADR > ADR
  - Tolerable
  - Safe

Trials of 4L vs. 2L PEG

Outcome	No. trials	No. patients	No. validated
Bowel cleanliness	23	5533	14 (61%)
Tolerability	13	3299	0
Safety (electrolyte)	6	1325	N/A
Polyp detection	5	987	N/A

Bowel cleanliness



Study or Subgroup	2L PEG Events	2L PEG Total	4L PEG Events	4L PEG Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Day before for 4L vs 2L						
Adams 1994	131	191	128	191	5.4%	1.02 [0.89, 1.18]
Gentile 2011	30	60	30	60	2.0%	1.00 [0.70, 1.43]
McKenna 2012	54	66	59	70	5.0%	0.97 [0.83, 1.13]
Ponchon 2013	177	210	172	205	6.7%	1.00 [0.92, 1.09]
Pontone 2011	37	72	30	72	2.0%	1.23 [0.87, 1.76]
Samarasena 2012	19	60	11	57	0.7%	1.64 [0.86, 3.14]
Sharma 2008	76	91	46	59	4.8%	1.07 [0.91, 1.26]
Valiante 2012	143	169	128	170	6.1%	1.12 [1.01, 1.25]
Subtotal (95% CI)		**919**		**884**	**32.6%**	**1.04 [0.99, 1.10]**
Total events	667		604			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.77$, df = 7 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 1.62 (P = 0.11)						
1.2.2 Split dose 4L vs 2L						
Corporaal 2010	135	149	151	158	7.1%	0.95 [0.89, 1.01]
Ell 2008	156	180	162	179	6.9%	0.96 [0.89, 1.03]
Hjelkrem 2011	35	213	49	101	1.9%	0.34 [0.24, 0.49]
Samarasena 2012	41	54	42	51	4.1%	0.92 [0.76, 1.12]
Subtotal (95% CI)		**596**		**489**	**20.0%**	**0.79 [0.64, 0.99]**
Total events	367		404			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 46.25$, df = 3 (P < 0.00001); $I^2 = 94\%$						
Test for overall effect: Z = 2.02 (P = 0.04)						
1.2.3 Day before 4L vs same day 2L						
Abut 2009	22	39	44	81	2.1%	1.04 [0.74, 1.46]
Di Palma 2003	81	100	86	100	5.7%	0.94 [0.83, 1.07]
Park 2010	55	95	40	95	2.6%	1.38 [1.03, 1.84]
Subtotal (95% CI)		**234**		**276**	**10.4%**	**1.08 [0.83, 1.42]**
Total events	158		170			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 7.04$, df = 2 (P = 0.03); $I^2 = 72\%$						
Test for overall effect: Z = 0.59 (P = 0.55)						
1.2.4 Split dose 4L vs same day 2L						
Cesaro 2011	35	50	24	51	2.1%	1.49 [1.06, 2.10]
Park 2010	55	95	61	95	3.5%	0.90 [0.72, 1.13]
Seo 2013	72	103	75	102	4.6%	0.95 [0.80, 1.13]
Subtotal (95% CI)		**248**		**248**	**10.2%**	**1.04 [0.82, 1.34]**
Total events	162		160			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.33$, df = 2 (P = 0.04); $I^2 = 68\%$						
Test for overall effect: Z = 0.35 (P = 0.73)						
1.2.5 Complex regimen						
Haapamaki 2011	145	244	144	246	5.1%	1.02 [0.88, 1.18]
Huppertz-Haus 2005	40	71	62	76	3.5%	0.69 [0.55, 0.87]
Jansen 2011	149	188	141	182	6.1%	1.02 [0.92, 1.14]
Kao 2011	174	214	170	218	6.4%	1.04 [0.95, 1.15]
Mathus-Vliegen 2013	78	100	90	100	5.7%	0.87 [0.77, 0.98]
Subtotal (95% CI)		**817**		**822**	**26.8%**	**0.94 [0.84, 1.05]**
Total events	586		607			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 15.05$, df = 4 (P = 0.005); $I^2 = 73\%$						
Test for overall effect: Z = 1.05 (P = 0.29)						
Total (95% CI)		**2814**		**2719**	**100.0%**	**0.98 [0.92, 1.04]**
Total events	1940		1945			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 74.02$, df = 22 (P < 0.00001); $I^2 = 70\%$						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: $Chi^2 = 7.72$, df = 4 (P = 0.10), $I^2 = 48.2\%$						

Risk Ratio M-H, Random, 95% CI

0.2 0.5 1 2 5

Favors PEG 4L Favors PEG 2L

FARNCOMBE

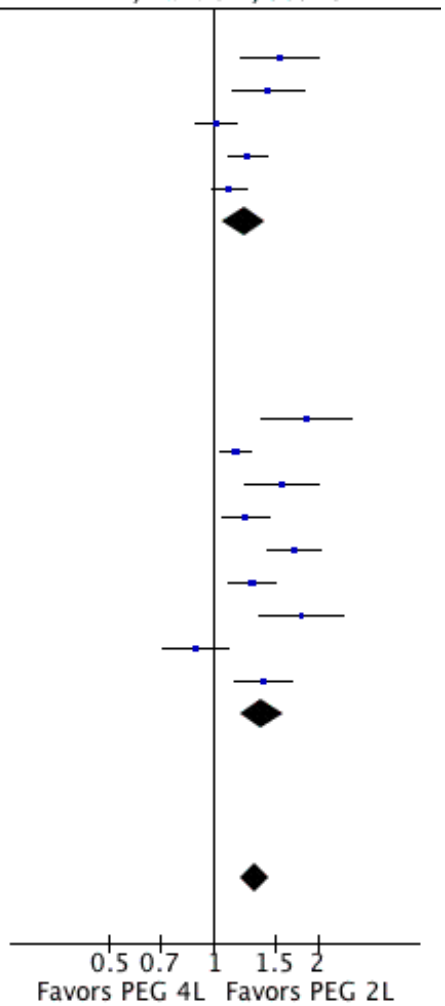
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

Tolerability

Study or Subgroup	2L PEG Events	2L PEG Total	4L PEG Events	4L PEG Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Adjectival scale						
Adams 1994	93	191	60	191	6.0%	1.55 [1.20, 2.00]
Di Palma 2003	70	100	49	100	6.3%	1.43 [1.13, 1.81]
Enestvedt 2011	71	87	83	103	8.1%	1.01 [0.88, 1.16]
Haapamaki 2011	181	244	146	246	8.3%	1.25 [1.10, 1.42]
Valiante 2012	138	169	126	170	8.5%	1.10 [0.98, 1.23]
Subtotal (95% CI)		**791**		**810**	**37.3%**	**1.22 [1.06, 1.41]**
Total events	553		464			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 15.86$, df = 4 (P = 0.003); $I^2 = 75\%$						
Test for overall effect: Z = 2.74 (P = 0.006)						
1.1.2 Willingness to have same preparation						
Cesaro 2011	47	52	25	51	5.3%	1.84 [1.37, 2.47]
Enestvedt 2011	83	87	85	103	8.8%	1.16 [1.05, 1.28]
Kao 2011	105	210	67	210	6.2%	1.57 [1.23, 1.99]
Ker 2006	113	150	92	150	7.8%	1.23 [1.05, 1.44]
Mathus-Vliegen 2013	95	100	56	100	7.4%	1.70 [1.42, 2.03]
McKenna 2012	62	66	51	70	7.8%	1.29 [1.10, 1.51]
Park 2010	68	95	38	95	5.6%	1.79 [1.36, 2.36]
Pontone 2011	47	72	53	72	6.6%	0.89 [0.71, 1.10]
Seo 2013	84	103	60	102	7.2%	1.39 [1.15, 1.67]
Subtotal (95% CI)		**935**		**953**	**62.7%**	**1.37 [1.19, 1.58]**
Total events	704		527			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 43.18$, df = 8 (P < 0.00001); $I^2 = 81\%$						
Test for overall effect: Z = 4.37 (P < 0.0001)						
Total (95% CI)		**1726**		**1763**	**100.0%**	**1.31 [1.19, 1.45]**
Total events	1257		991			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 63.70$, df = 13 (P < 0.00001); $I^2 = 80\%$						
Test for overall effect: Z = 5.28 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 1.31$, df = 1 (P = 0.25), $I^2 = 23.6\%$						

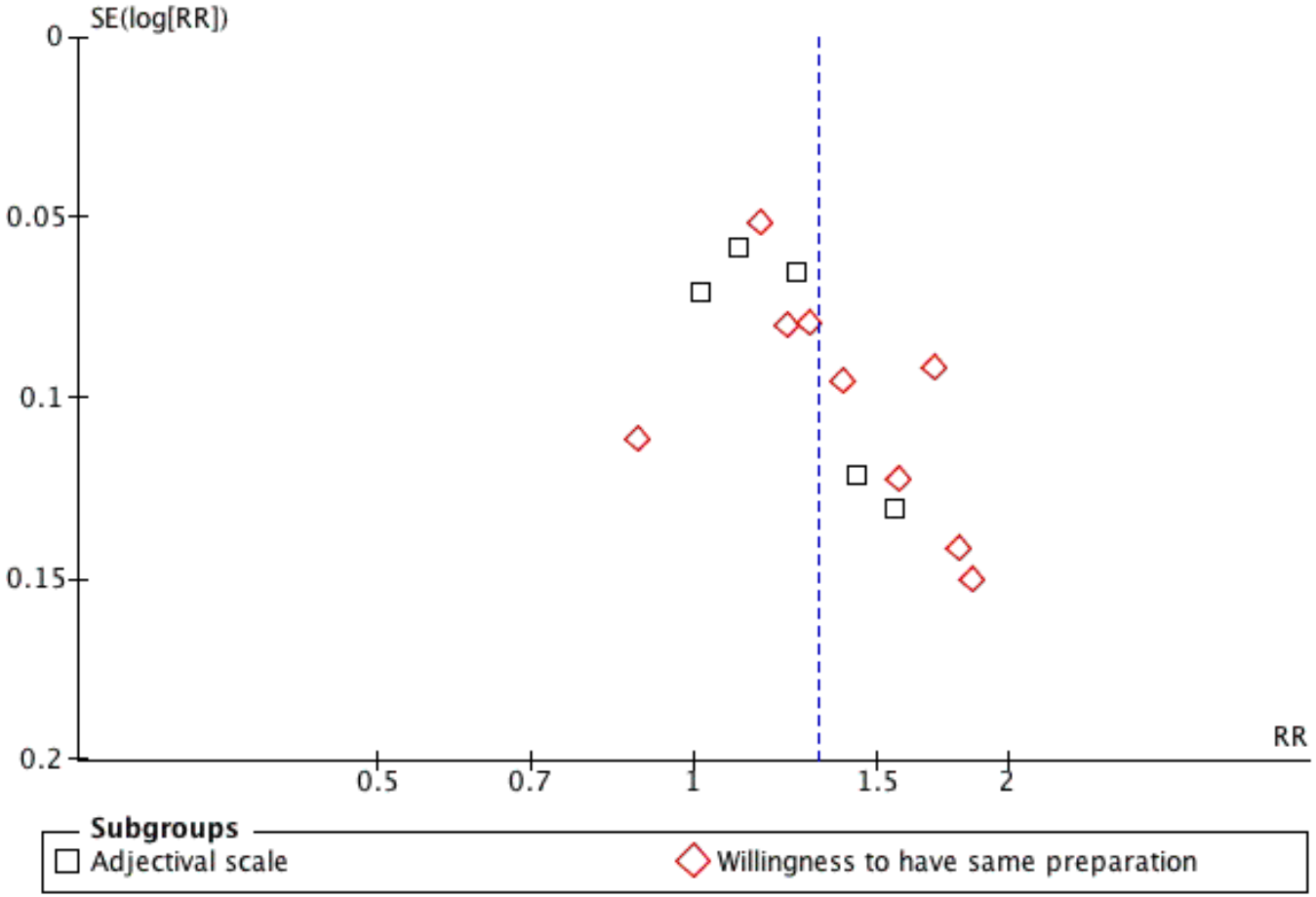


FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

Funnel plot of tolerability trials



Egger test – p = 0.02

FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

Confidence assessment criteria
Tolerability of 2L vs. 4L

Study Design	Confidence in estimates	Lower if	Higher if
Randomised trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or
	Very low	Imprecision -1 Serious -2 Very serious	+1 Would suggest a spurious effect when results show no effect
		Publication bias -1 Likely -2 Very likely	

FARNCOMBE
Farncombe Family Digestive Health Research Institute

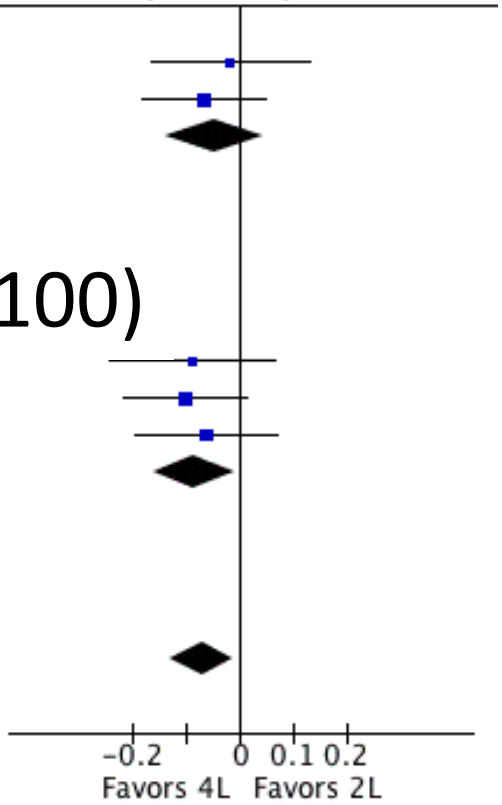
McMaster University

THE COCHRANE COLLABORATION®

Polyp detection rates: 2L vs. 4L PEG

Study or Subgroup	2L PEG Events	2L PEG Total	4L PEG Events	4L PEG Total	Weight	Risk Difference M-H, Random, 95% CI
1.3.1 Any polyp						
Abut 2009	7	39	16	81	15.4%	-0.02 [-0.17, 0.13]
Hjelkrem 2011	90	213	52	106	25.2%	-0.07 [-0.18, 0.05]
Subtotal (95% CI)		**252**		**187**	**40.6%**	**-0.05 [-0.14, 0.04]**
Total events	97		68			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.28$, df = 1 (P = 0.59); $I^2 = 0\%$						
Test for overall effect: Z =						
1.3.2 Adenoma						
Cesaro 2011	25	102	17	51	14.3%	-0.09 [-0.24, 0.07]
Enestvedt 2011	14	87	27	103	25.7%	-0.10 [-0.22, 0.01]
Seo 2013	35	103	41	102	19.4%	-0.06 [-0.19, 0.07]
Subtotal (95% CI)		**292**		**256**	**59.4%**	**-0.09 [-0.16, -0.01]**
Total events	74		85			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.20$, df = 2 (P = 0.91); $I^2 = 0\%$						
Test for overall effect: Z = 2.22 (P = 0.03)						
Total (95% CI)		**544**		**443**	**100.0%**	**-0.07 [-0.13, -0.01]**
Total events	171		153			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.82$, df = 4 (P = 0.94); $I^2 = 0\%$						
Test for overall effect: Z = 2.38 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 0.36$, df = 1 (P = 0.55), $I^2 = 0\%$						

NNT = 14 (95%CI = 8 to 100)



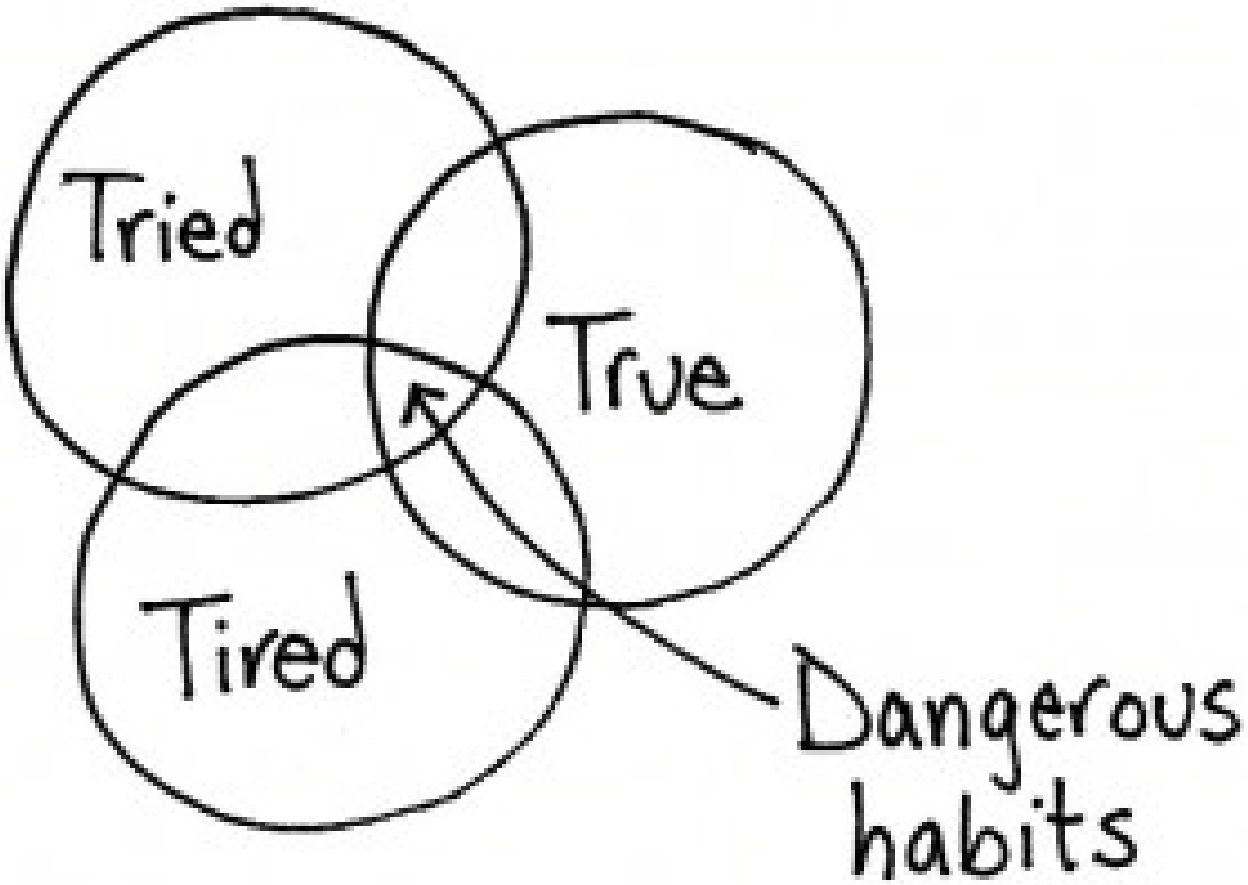
FARNCOMBE
Farncombe Family Digestive Health Research Institute

McMaster University

THE COCHRANE COLLABORATION®

Conclusions

- Use PEG or sodium picosalix
- Data on oral sulfate solution modest
- Split dose preparations (especially PEG)
- End points to date have been clinician focused
- More effort in making end points patient focused
- More rigorous appraisal of confidence in the estimate of effect.


Tried
True
Tired
Dangerous habits

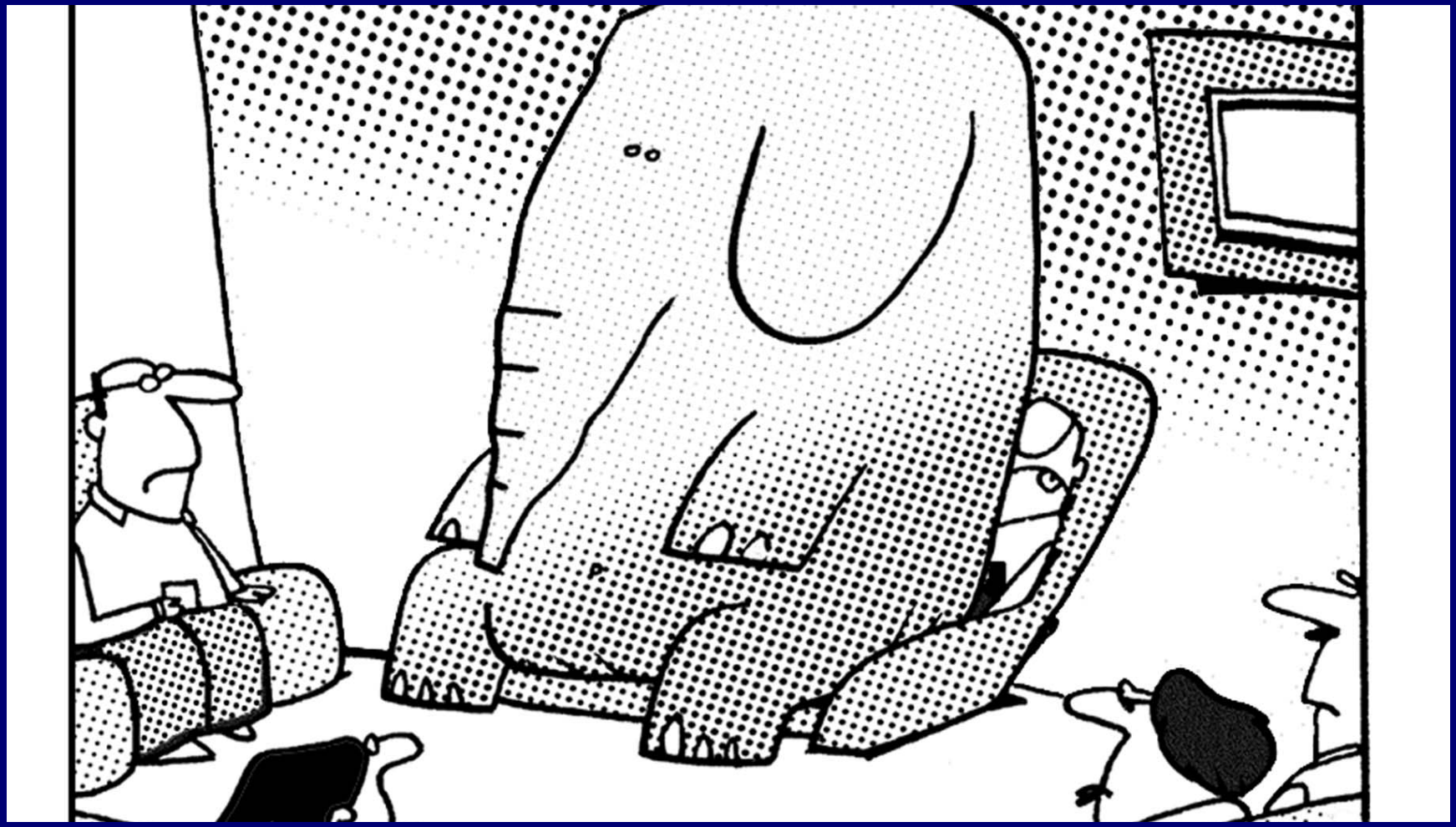
Safety Issues Surrounding Over-the-Counter and Prescription Bowel Preparations

Philip Schoenfeld, MD, MSEd, MSc (Epi)
Professor of Medicine
Director, Training Program in GI Epidemiology
U. of Michigan School of Medicine

Disclosures

- Consultant, Advisory Board Member and Speaker’s Bureau: Salix Pharmaceuticals, Ironwood Pharmaceuticals, Forest Laboratories

- Partner, EBMed, LLC,



… only Alan was prepared to acknowledge the elephant in the room..

Miralax – Gatorade Bowel Prep

+

238 gram
Bottle of MiraLAX

64 oz.
Bottle of Gatorade

plus 10-20mg bisacodyl

Advantages of Miralax-Gatorade

- Low volume
- Palatable
- Inexpensive

… may lead to improved complicance with bowel preparation regimen?

Increasing Popularity of Miralax-Gatorade Combination

- **Survey of random sample of ACG members in US in *2010-11***
- **Asked about use of split-dose, liberal diet (low residue on day before procedure), and use of Miralax-based preparations.**
- **30% of sample responded to survey (288/999)**
- **60% (170/283) used split-dose**
- ***37% (106/283) used miralax-based preps. Among these physicians, 82% (87/106) combined it with gatorade. Data based on survey from 2010-11.***

Hillyer G, Lebwohl B, Basch C, et al. Therapeutic Advances in Gastroenterology 2013; 6: 5-14

Miralax-Gatorade Bowel Preparation

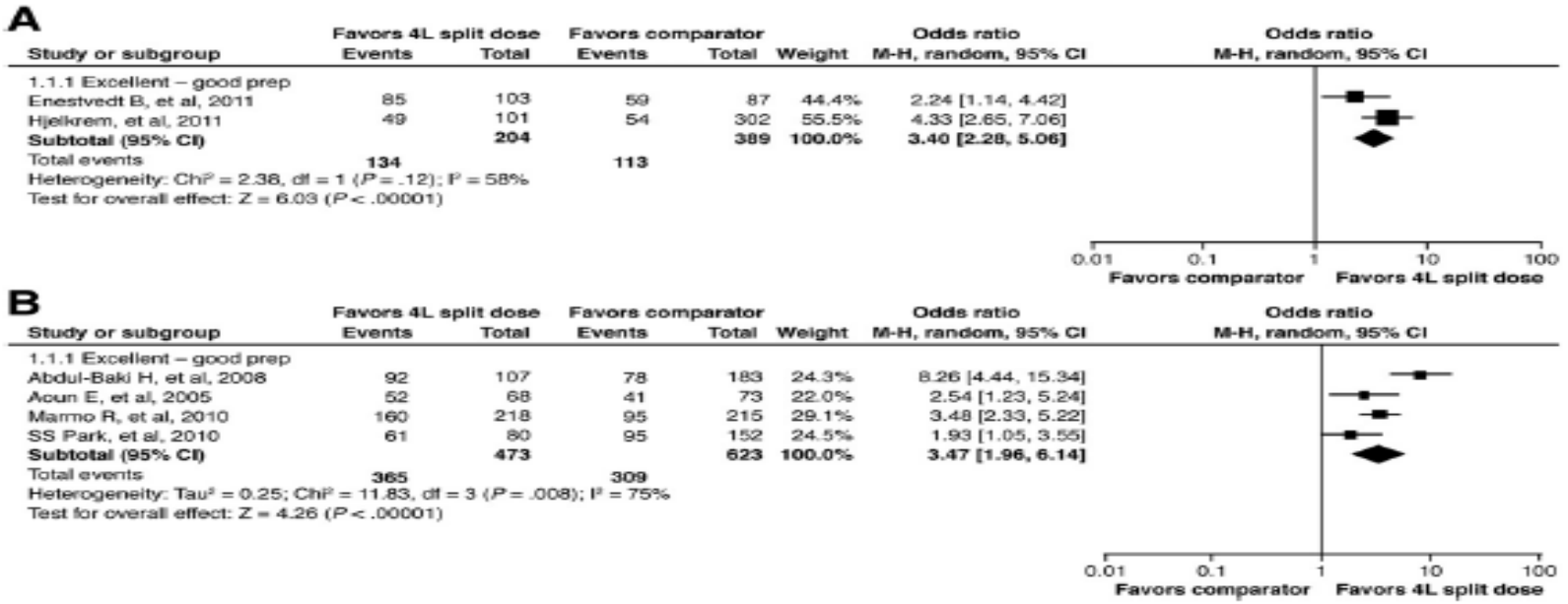


Figure 3. Post hoc subgroup meta-analyses showing a higher number of excellent or good bowel preparations with 4-L split-dose PEG than for (*A*) MiraLAX/Gatorade or (*B*) single-dose 4-L PEG preparations. (A) A 4-L split-dose PEG vs MiraLAX/Gatorade. (B) A 4-L split-dose PEG vs single-dose PEG.

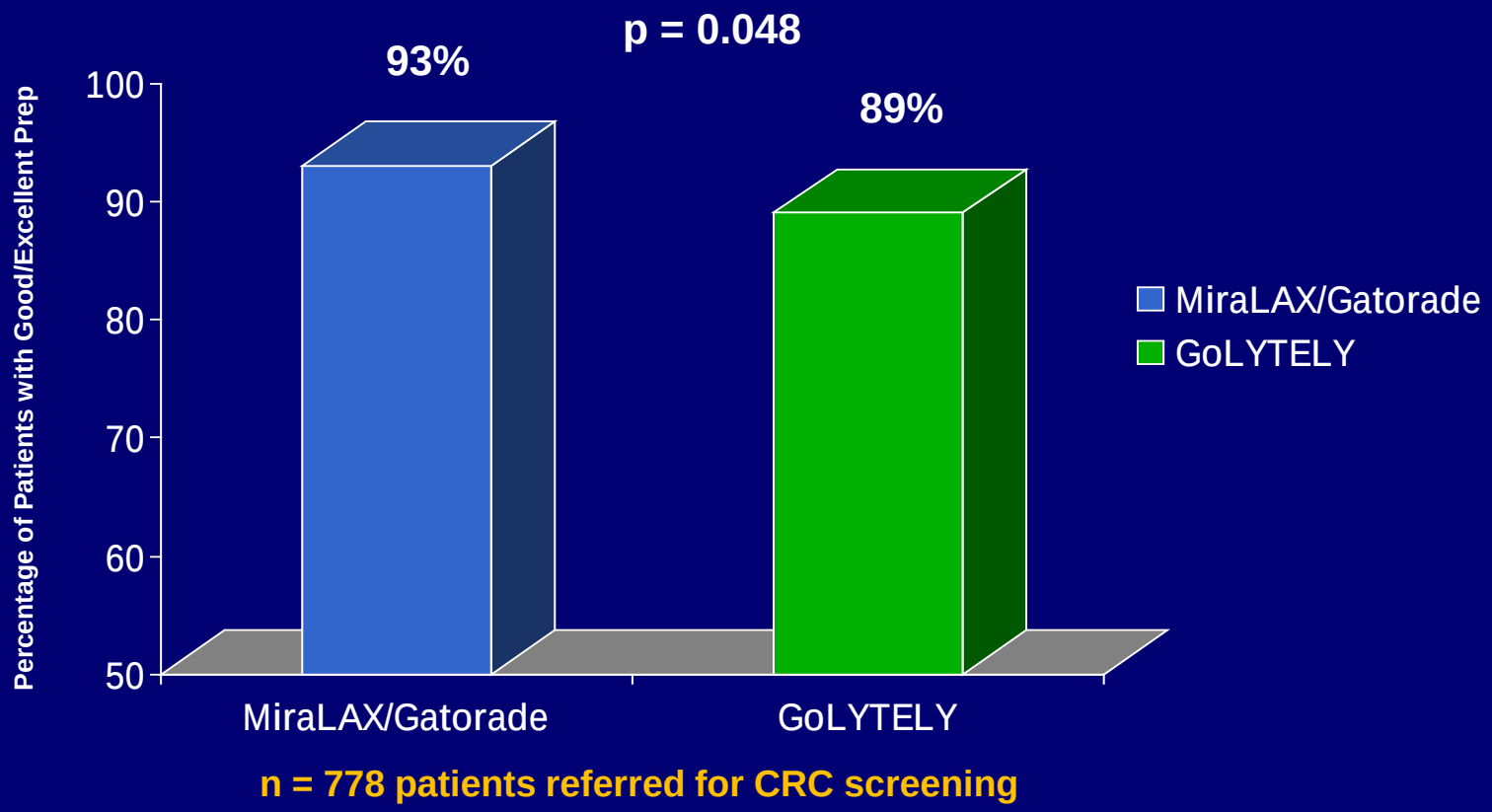
OR = 3.40 (2.28-5.06) for Excellent/Good Bowel Cleansing with split-dose 4l Golytely vs split-dose MiraLax-Gatorade

this is the same as OR for getting Excellent/Good Bowel Cleansing with 4l of Golytely split-dose vs 4l Golytely as pm single dose (OR =3.47; 1.96-6.14)

For Enestvedt RCT, rate of excellent or good prep by Boston Bowel Prep Score was 83% (85/103) vs 68% (59/87)

Enestvedt BK, et al. Clin Gastro Hepatol 2012; 10: 1225

Retrospective Endoscopic Database Analysis: PEG-3350 + Gatorade + Bisacodyl vs. 4-L GoLYTELY



Shieh F, Schoenfeld P, et al. *Gastrointest Endosc* 2008; W1543.
Shieh F, Schoenfeld P, et al. J Clin Gastroenterol 2012; 46: e96-e100

Similarities between Miralax-Gatorade & Fleets Phospho-Soda

- Low volume
- Palatable
- No prescription needed*

**Cost for M-G plus dulcolax and 4L generic PEG is quite similar at appoximately $15 for both.*

Similarities between Miralax-Gatorade & Fleets Phospho-Soda

- Low volume
- Palatable
- No prescription needed*

- Hyperosmolar
- Not FDA approved
- Minimal safety data

**Cost for M-G plus dulcolax and 4L generic PEG is quite similar at appoximately $15 for both.*

Similarities between Miralax-Gatorade & Fleets Phospho-Soda

- Low volume
- Palatable
- No prescription needed

- Hyperosmolar
- Not FDA approved
- Minimal safety data

- *Commonly used at 14X approved FDA-dose (for constipation) when used as bowel preparation*

Electrolytes in Sports Drinks May Be Insufficient

Although sports drinks can aid in rehydrating and replacing electrolytes lost during sweating as a result of physical exertion, the electrolyte load may be insufficient for patients undergoing a purgative regimen for colonoscopy

	Sports drink, g/2 L*	PEG + ELS, g/2 L	Ratio (PEG + ELS:Sports drink)
Sodium	0.88	8.35	9:1
Potassium	0.24	1.06	4:1
Chloride	0.72	4.23	6:1

PEG + ELS = polyethylene glycol electrolyte lavage solution.
***Traditional Gatorade®.**
Cohen et al. *Gastroenterol Hepatol*. 2009;5(11; suppl 20):1-11.

Severe Hyponatremia and Seizure Following a Polyethylene Glycol-based Bowel Preparation for Colonoscopy

To the Editor:

Instances of hyponatremia, seizure, and even death associated with both sodium phosphate and polyethylene glycol oral colonoscopy preparation solutions have been reported to the Food and Drug Administration, but no causative explanations were given.[1,2] Only 3 detailed case reports of hyponatremia due to bowel cleansing have been published, but none of the subjects who developed a seizure had used polyethylene glycol, which is believed to affect serum electrolytes minimally.[3–5] We report the case of an elderly woman who developed severe hyponatremia resulting in a generalized tonic-clonic seizure shortly after a polyethylene glycol-based bowel cleansing for colonoscopy. We wish to emphasize multiple contributing factors, some of which may be avoidable.

S.M., a 73-year-old woman, ingested 64 ounces of Gatorade into which she mixed 255 g of polyethylene glycol 3350 (Miralax) in preparation for a colorectal cancer screening colonoscopy examination. After drinking this mixture, she experienced abdominal discomfort and nausea. She vomited and feeling thirsty afterwards, swallowed 2 glasses of water. She was subsequently brought to our emergency department where her physical examination was normal except for tangential mentation with perseveration. No orthostatic changes were present. Very shortly afterwards, she developed a tonic-clonic seizure which was treated with intravenous lorazepam.

Past medical history was notable for hypothyroidism and depression. Outpatient medications included levothyroxine sodium and citalopram. Laboratory data revealed: serum sodium 117 mmol/L, potassium 3.3 mmol/L, chloride 79 mmol/L, bicarbonate 21 mmol/L, blood urea nitrogen 6 mg/dL, creatinine 0.6 mg/dL, serum osmolality 225, urine osmolality 390, urine sodium 146 mmol/L, and urine potassium 35.7 mmol/L. Her calculated FeNa was 3.8%.

Following an infusion of 1 L of 2% hypertonic saline, her serum sodium rose to 125 mmol/L. She was then placed on 1 L/d fluid restriction. When her serum sodium failed to rise higher, sodium chloride tablets, 1 g every 6 hours, were added. Further evaluation revealed a slightly elevated serum TSH level which was corrected by increasing her daily dose of levothyroxine. Oral sodium supplementation and fluid restriction were discontinued when her serum sodium rose to 131 mmol/L. Two weeks later as an outpatient, serum sodium was 138 mmol/L and her mental status was normal.

Hyponatremia, defined as a serum sodium less than 135 mmol/L, can be caused by salt loss secondary to vomiting, diarrhea or excessive perspiration and renal disease, hypoadrenalism, and hypothyroidism, but is most commonly due to the syndrome of inappropriate antidiuretic hormone release (SIADH). The regulation of free water clearance is dependent upon serum osmolality and is controlled via release of antidiuretic hormone (ADH). However, ADH release can also occur independently of osmolar stimuli in the presence of nausea, anxiety, or pain.[6,7] Age is another contributing factor. A study of 50 hospitalized patients with SIADH revealed that in 60% of cases, no cause for increased ADH other than advanced age (77 ± 8.3) could be identified.[8]

A variety of tumors, pulmonary diseases, and central nervous system disorders can cause an inappropriate release of ADH. Commonly prescribed medications such as thiazide diuretics, nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, and opiate derivatives are capable of raising ADH levels. Antidepressants of the selective serotonin re-uptake inhibitor (SSRI) class have become increasingly popular and may also cause hyponatremia via SIADH, especially in the elderly. In one study of 15 patients, 40% developed hyponatremia following a 2-week course of treatment with an SSRI.[9] Another study of 116 consecutive cases of hyponatremia in elderly patients (mean age 73) found that 75% of cases were secondary to the use of an SSRI.[10]

For the patient described in this report, her advanced age, the nausea, and cramps which followed her bowel preparation, and her use of an SSRI, may have led to SIADH. The addition of vomiting, pure water ingestion and inadequately treated hypothyroidism were further aggravating factors which ultimately resulted in severe hyponatremia and seizure. We conclude that physicians should become thoroughly familiar with a patient's medical history and current medications before prescribing a bowel cleansing regimen, all patients should be encouraged to keep well hydrated with electrolyte containing solutions both during and after laxative ingestion, and serum electrolytes should be checked if there are any mental aberrations before colonoscopy procedures.

Jerry Nagler, MD*
David Poppers, MD, PhD*
Meredith Turetz, MD†
*Department of Medicine
Division of Gastroenterology and Hepatology
†Department of Medicine
Division of Pulmonary Diseases
Weill Medical College of Cornell University
New York, NY

REFERENCES

1. Mackey AC, Schaffer D, Prizant R. Seizure associated with the use of visicol for colonoscopy. *N Engl J Med.* 2002;346:2095.
2. Rose M, Jacob LS. Seizure associated with the use of visicol for colonoscopy. *N Engl J Med.* 2002;347:295–296.
3. Salik JM, Kurtin P. Severe hyponatremia after colonoscopy preparation in a patient with the acquired immune deficiency syndrome. *Am J Gastroenterol.* 1985;80:177–179.
4. Schroppel B, Segerer S, Keuneke C, et al. Hyponatremia encephalopathy after preparation for colonoscopy. *Gastrointest Endosc.* 2001;53:529–530.
5. Frizelle FA, Colls BM. Hyponatremia and seizures after bowel preparation: report of three cases. *Dis Colon Rectum.* 2005;48:393–396.

First case report of severe hyponatremia with M-G prep

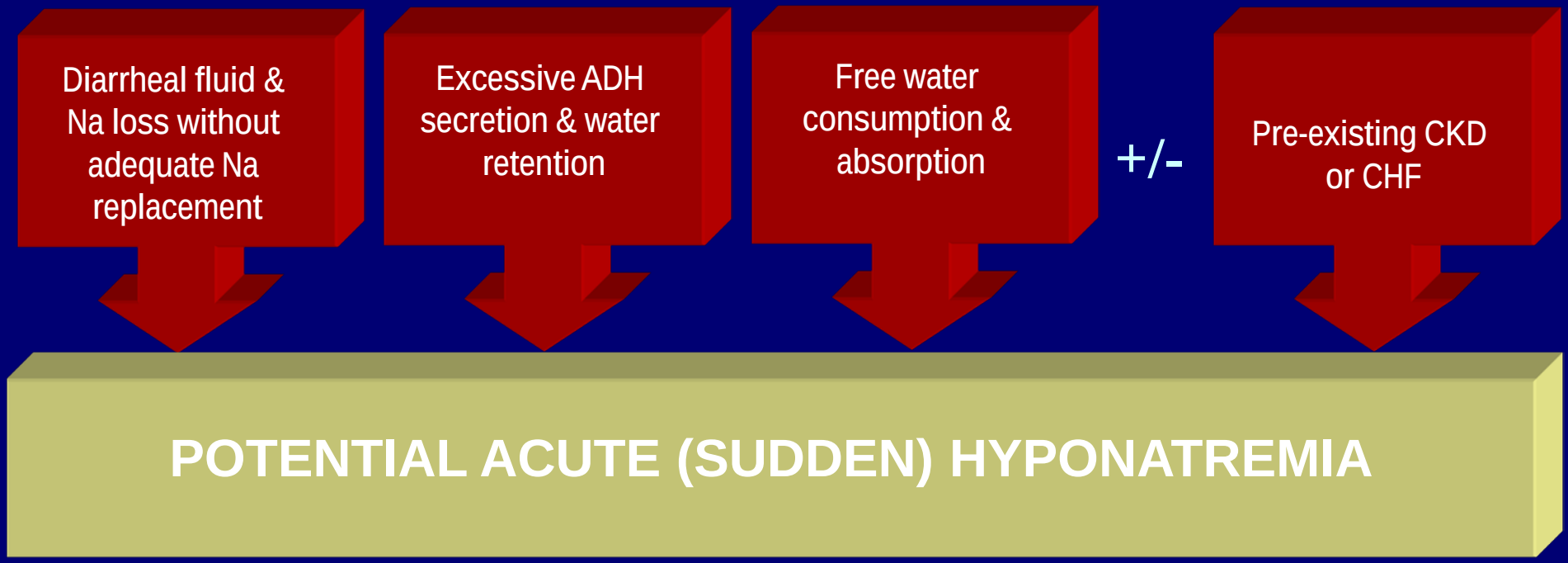
- **73-year-old-woman**
- **Severe hyponatremia (Na+ = 117 mmol/l)**
- **Hospitalized after generalized tonic-clonic seizure**

Nagler J et al. J Clin Gastro 2006; 40: 558

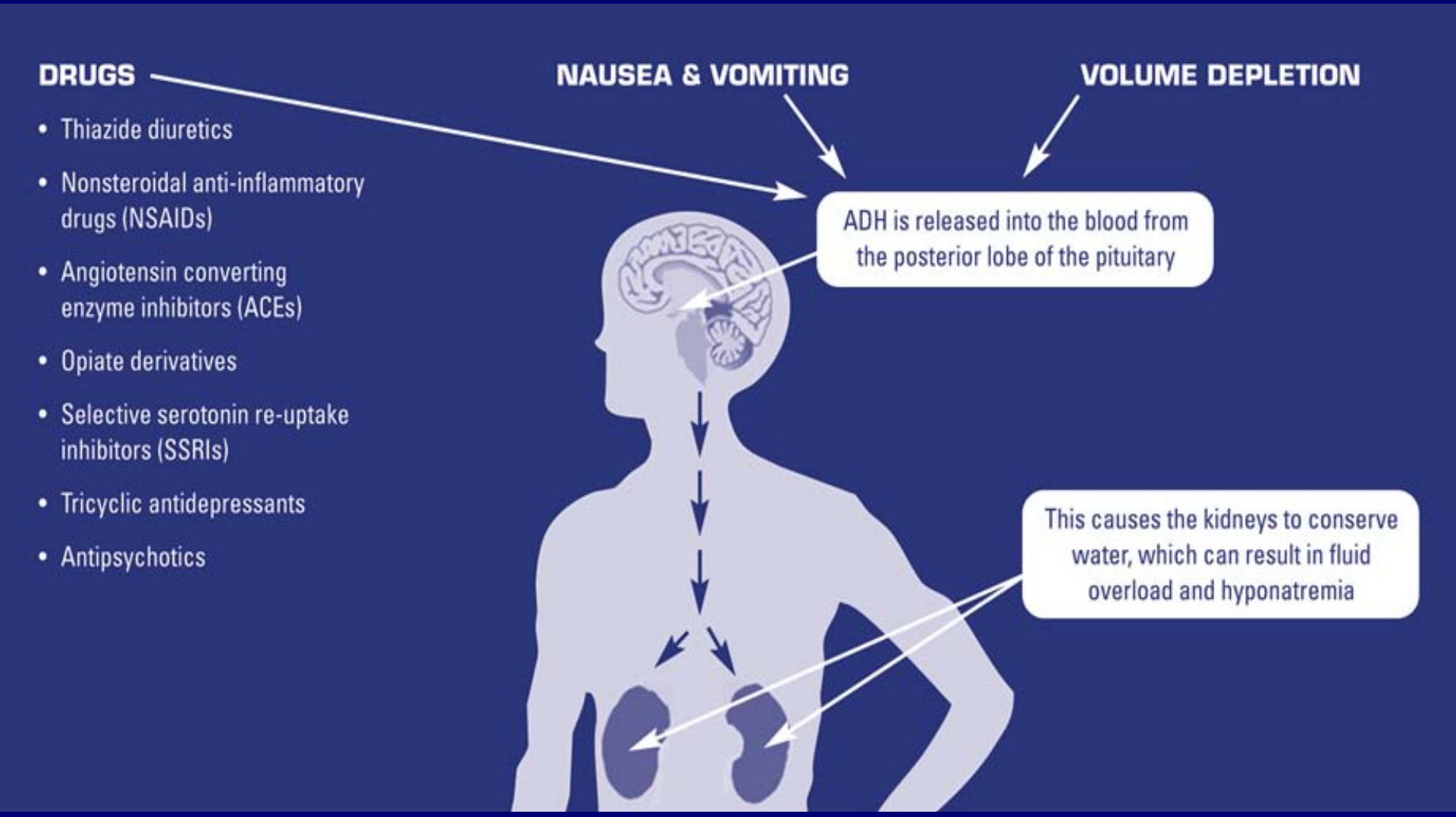
* All purgative products have been associated with hyponatremia and seizure. See full prescribing information for complete details.
MiraLAX is a registered trademark of Schering-Plough Healthcare Products, Inc.

Hyponatremia may develop with any colonoscopy preparation as a result of vomiting, diarrhea, renal disease, or inappropriate secretion of ADH (SIADH)

Physiological bases for potential hyponatremia OTC PEG-3350 + sports drink prep

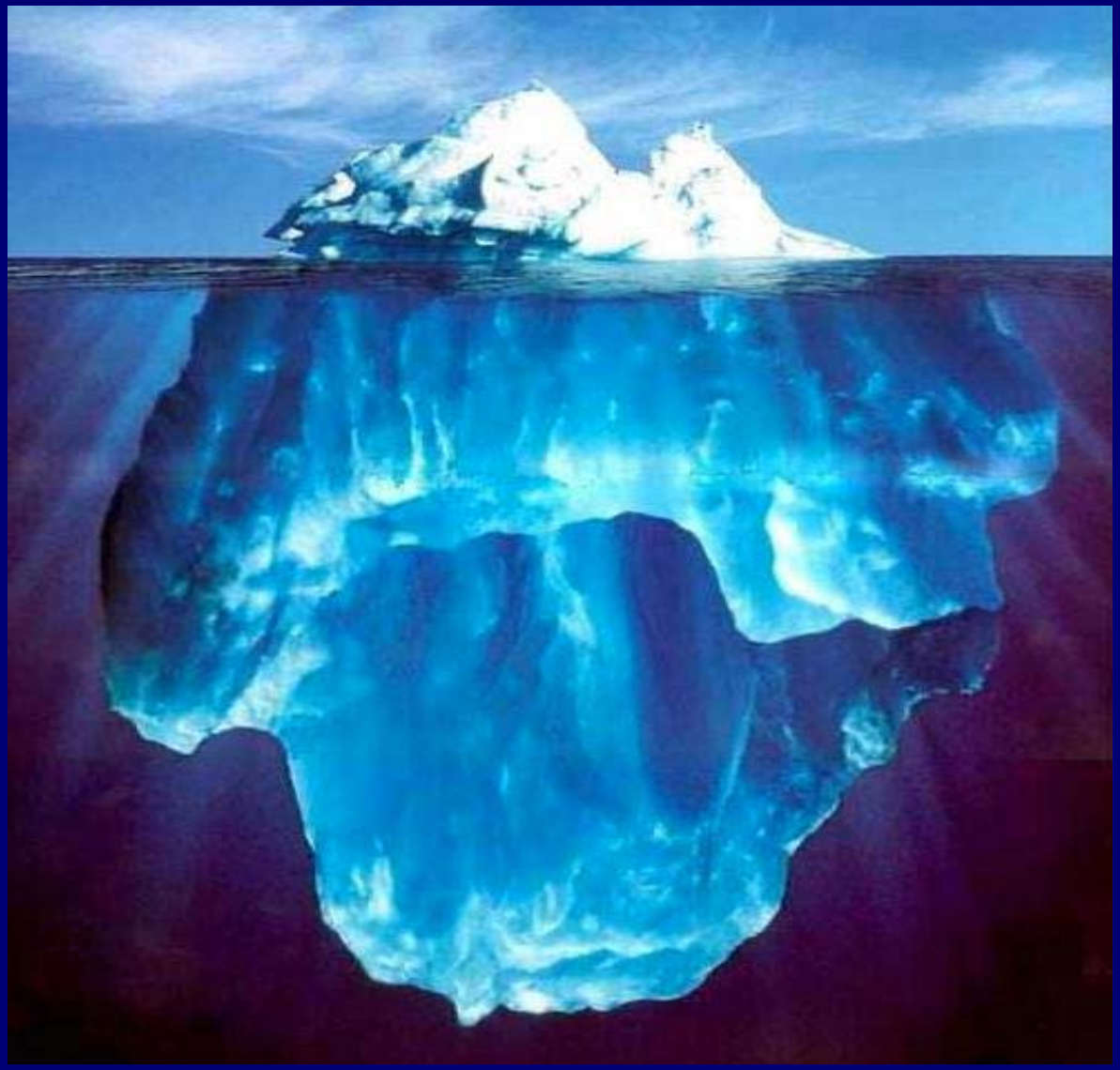


Possible Mechanism: SIADH



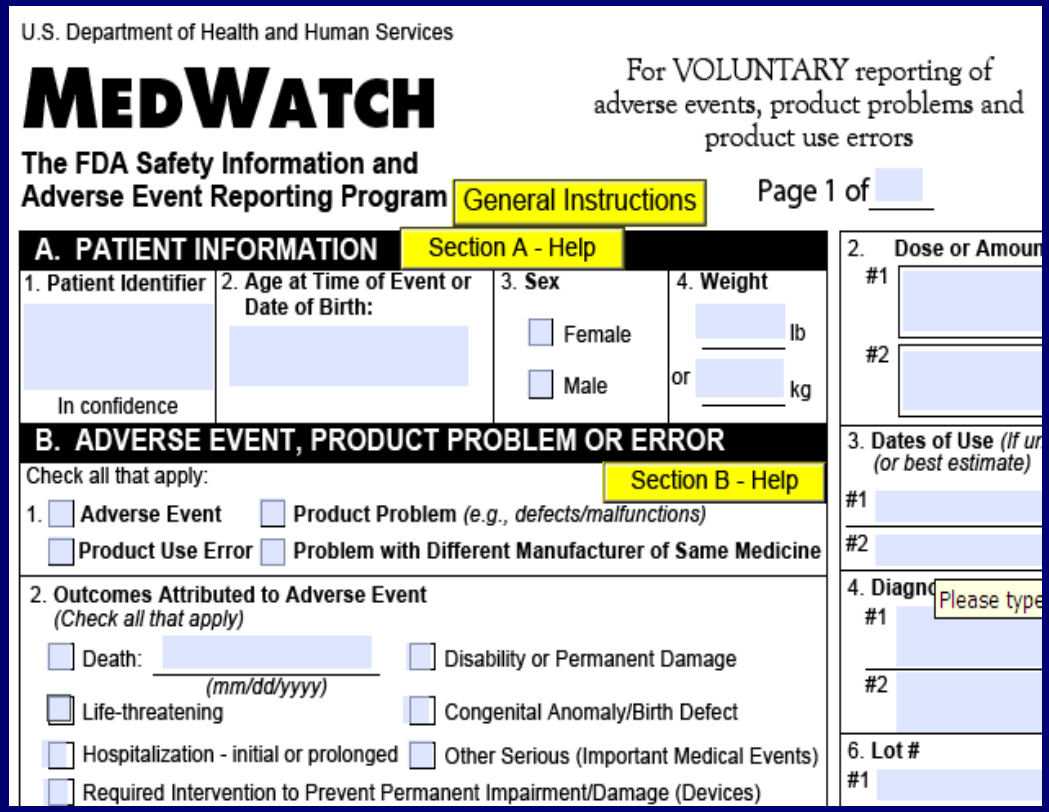
Three Cases of Severe Hyponatremia (< 130 mEq/l) with MiraLAX-Gatorade Use at UM in Summer 2010

Three Cases of Severe Hyponatremia (< 130 mEq/l) with MiraLAX-Gatorade Use at UM in Summer 2010



Methods

- Monitor for new adverse events in currently marketed drugs.
- Voluntary reporting.
- Physician/Nurse/Pharmacist
- Patients



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

General Instructions

Page 1 of

A. PATIENT INFORMATION Section A - Help

1. Patient Identifier — In confidence
2. Age at Time of Event or Date of Birth:
3. Sex — Female / Male
4. Weight — lb or kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR Section B - Help

Check all that apply:

1. Adverse Event / Product Problem *(e.g., defects/malfunctions)* / Product Use Error / Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*

Death: _____ *(mm/dd/yyyy)* / Disability or Permanent Damage / Life-threatening / Congenital Anomaly/Birth Defect / Hospitalization - initial or prolonged / Other Serious (Important Medical Events) / Required Intervention to Prevent Permanent Impairment/Damage (Devices)

2. Dose or Amoun
#1
#2

3. Dates of Use *(If ur (or best estimate)*
#1
#2

4. Diagnc Please type
#1
#2

6. Lot #
#1

Results

- **14 identified cases by May 15 2011
- All outpatient colonoscopies
- Age: range 35-76 y/o
- Gender: 12:2 - Female: Male ratio
- No sig PMHx = 6; Htn = 3; Hypothyroid = 2, No Data = 3
- Symptomatic Presentation: Nausea, Vomiting, Syncope
- 29% (4/14) hospitalized in ICU setting
- Lowest reported Na (range): 117 – 128 mEQ/mL

Lewis JL, Schoenfeld PS. *Am J Gastroenterol* 2011; 106 (suppl 2): p. s582; A1524.

… but it isn't all bad news

- RCT of pm only M-G (n=66) vs 2L PEG-ELS (MoviPrep ®) (n=70) with serum electrolytes on day of colonoscopy[1]
  - Serum Na+: 138.8(+/- 2.4) mmol/L vs 139.3 (+/- 2.4) mmol/L; p =0.13

- RCT of 222 patients randomized to split dose M-G (n = 54); pm only M-G (n = 60); split-dose 4L GoLytely (n=51); pm only 4L GoLytely (n = 57)[2]
  - Serum electrolytes obtained before start of bowel preparation & before colonoscopy.
  - No significant differences in mean change in electrolytes from baseline in any group. Range of change in sodium: -0.37 (pm only M-G) to +0.02 (pm only GoLyely)

- RCT of 389 patients randomized to split dose M-G (n=180) vs split dose PEG-ELS (MoviPrep®) (n= 184)[3]
  - Serum electrolytes obtained before start of bowel preparation & before colonoscopy.
  - Hyponatremia: M-G = 3.9% (7/180) vs PEG-ELS 2.2% (4/184); OR = 1.8; 0.5-8.6; p=0.38)

1. McKenna T, et al. Dig Dis Sci 2012; 57: 3098-3105
2. Samarsena J, et al. Am J Gastroenterol 2012; 107: 1036-42.
3. Matro R, Kastenberg D, et al. Aliment Pharmacol Ther 2014; 40: 610-19

… but it isn't all bad news

- RCT of pm only M-G (n=66) vs 2L PEG-ELS (MoviPrep ®) (n=70) with serum electrolytes on day of colonoscopy[1]
  - Serum Na+: 138.8(+/- 2.4) mmol/L vs 139.3 (+/- 2.4) mmol/L; p =0.13

- RCT of 222 patients randomized to split dose M-G (n = 54); pm only M-G (n = 60); split-dose 4L GoLytely (n=51); pm only 4L GoLytely (n = 57)[2]
  - Serum electrolytes obtained before start of bowel preparation & before colonoscopy.
  - No significant differences in mean change in electrolytes from baseline in any group. Range of change in sodium: -0.37 (pm only M-G) to +0.02 (pm only GoLyely)

- RCT of 389 patients randomized to split dose M-G (n=180) vs split dose PEG-ELS (MoviPrep®) (n= 184)[3]
  - Serum electrolytes obtained before start of bowel preparation & before colonoscopy.
  - Incidence of hyponatremia: M-G = 3.9% (7/180) vs PEG-ELS 2.2% (4/184); OR = 1.8; 0.5-8.6; p=0.38)

…But is this sample size large enough to identify a significant difference in rare serious adverse event?

1. McKenna T, et al. Dig Dis Sci 2012; 57: 3098-3105
2. Samarsena J, et al. Am J Gastroenterol 2012; 107: 1036-42.
3. Matro R, Kastenberg D, et al. Aliment Pharmacol Ther 2014; 40: 610-19

Increased Risk of Severe Hyponatremia with Miralax-Gatorade vs Iso-osmolar PEG solution

- IRB-approved retrospective database study
- Linked UM colonoscopy scheduling records to UM Emergency Dept records
- Identified individuals who presented to ED during the 24 hours prior to scheduled colonoscopy.

Schoenfeld P, Elliott E. Am J Gastroenterol 2011; 106: A1525

Increased Risk of Severe Hyponatremia with Miralax-Gatorade vs Standard Bowel Preparation

- **Among 8413 colonoscopies performed in 2009, 5 patients were hospitalized for severe hyponatremia:**

  0.13% (3/2304) of M-G pts vs 0.032% (2/6109) of PEG pts

  odds ratio = 3.98; 95% CI: 0.66-23.8; p = 0.10.

- **All patients presented with a combination of N/V, pre-syncope, mental status changes, or abd pain.**

Schoenfeld P, Elliott E. Am J Gastroenterol 2011; 106: A1525

… and it isn't just OTC products

- **Prepopik®: sodium picosulfate, mag oxide, & anhydrous citric acid) Hyperosmolar, FDA-approved.**
  - **Rex et al. Split-dose Prepopik® superior to pm only Half-lytely® for bowel cleansing. [1,2]**
  - **Hyponatremia more common with Prepopik®:**
    - **3.7%(11/298) vs 1% (3/295)**
    - **OR =3.73 (95% CI: 1.03-13.5;p =0.045)**

…. But this is asymptomatic hyponatremia! What about clinically important hyponatremia?

1. Rex D, et al. Gastrointest Endosc 2013; 78: 132-41.
2. Prepopik® Package Insert. Parsipanny, NJ. Ferring Pharmaceuticals, Inc. 2013

Risk of Hospitalization with Hyponatremia with Prepopik®

- **Population-based retrospective cohort study in Canada. Looked for hospitalization with hyponatremia within 30 days of prescription date.**

- **Risk of hyponatremia higher with sodium picosulfate bowel preparation (10mg sodium picosulfate, 3.5gm mag oxide & 12g citric acid per sachet) vs PEG bowel preparations:**

  - ***0.09% (93/99,237) vs 0.04% (20/48,595);***
  - ***adjusted RR = 2.4 (1.5-3.9);***
  - ***absolute risk difference 0.05 (95% CI: 0.04-0.06);***
  - ***NNH = 1903(95% CI: 1645-2257)***

1. Weir MA, et al. Am J Gastroenterol 2014; 109: 686-94

Conclusions

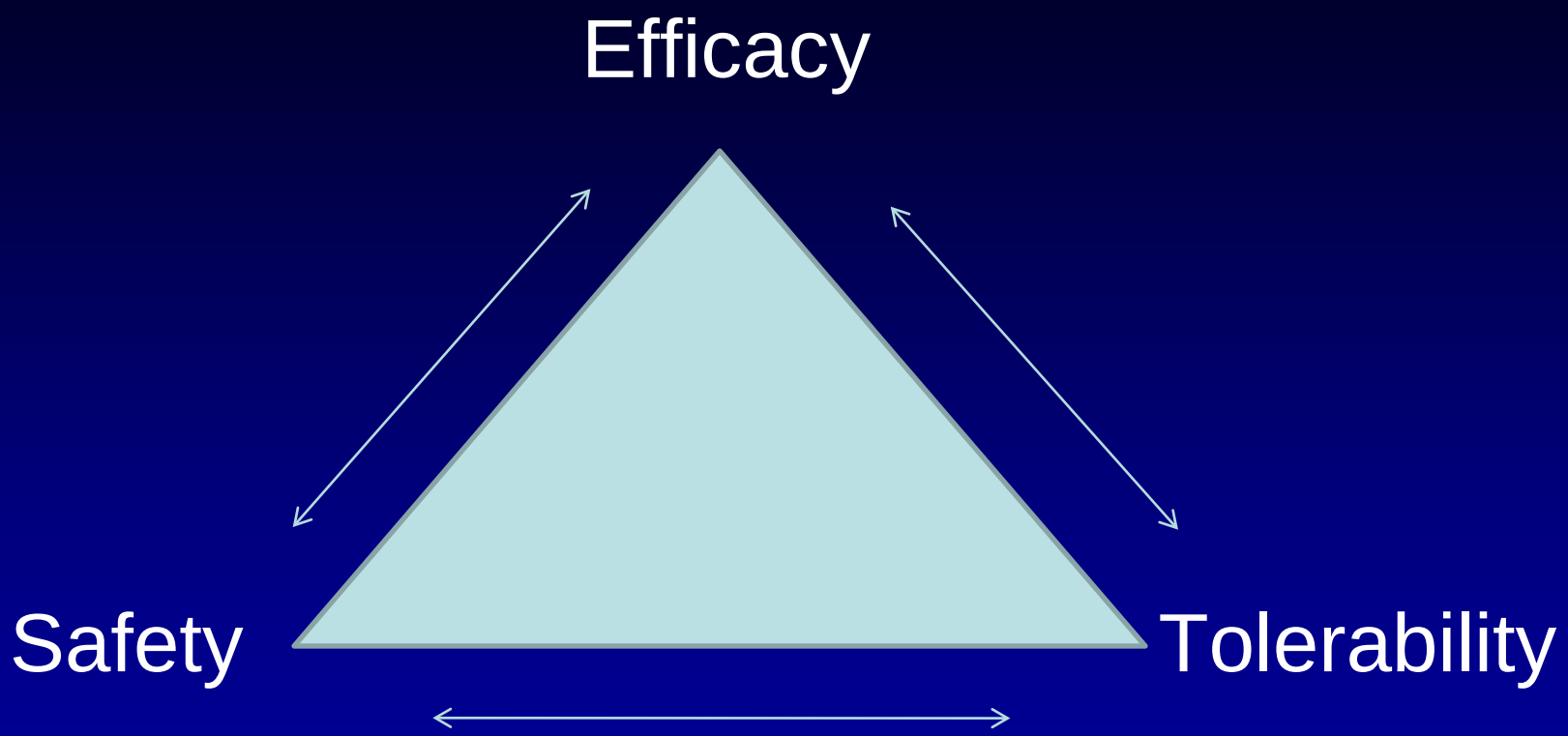
- **Hospitalization due to severe hyponatremia has occurred with Miralax-Gatorade Bowel Prep and has been associated with Prepopik®**
- **Caution should be used in recommending a non-FDA approved prep with limited safety data.**
- **Possible association between these bowel preps and severe hyponatremia requires confirmation through further research.**
- ***Remember: complications have been reported with all bowel preparations. No single bowel preparation is universally safe!***

The Clinician and Patient Perspective on Endpoints for Bowel Cleansing Studies

Douglas K Rex MD, MACG
Indiana University Health
Indianapolis, IN

Disclosures

- Past consultant to, research support from, and speaker's bureau member for Braintree and Ferring (no current or recent association)
- Braintree sponsors the ASGE colonoscopy "Tip of the Week" – all funding is to the ASGE


Efficacy
Safety
Tolerability

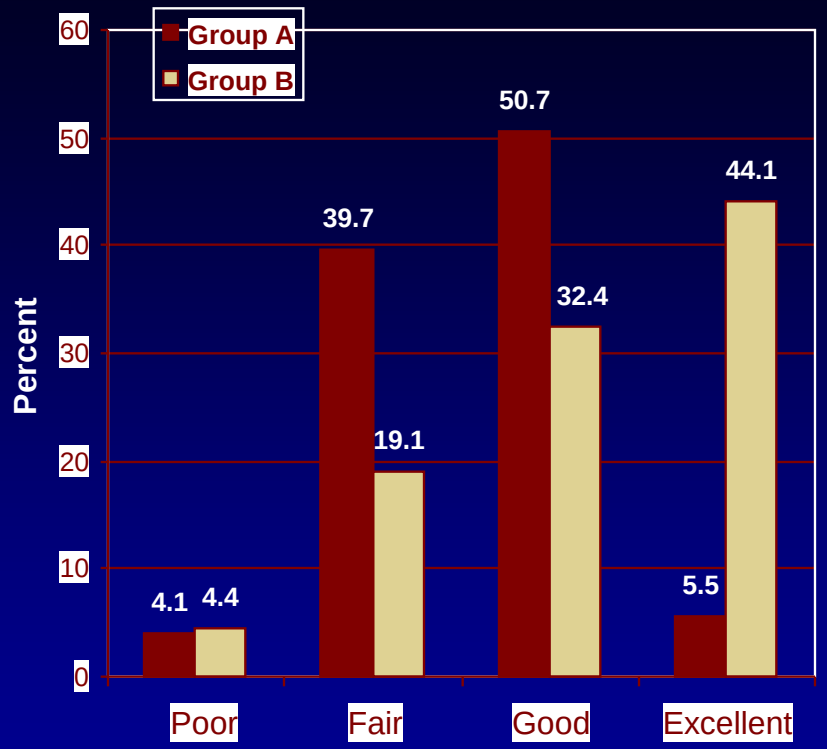
Safety, Efficacy, Tolerability Interaction

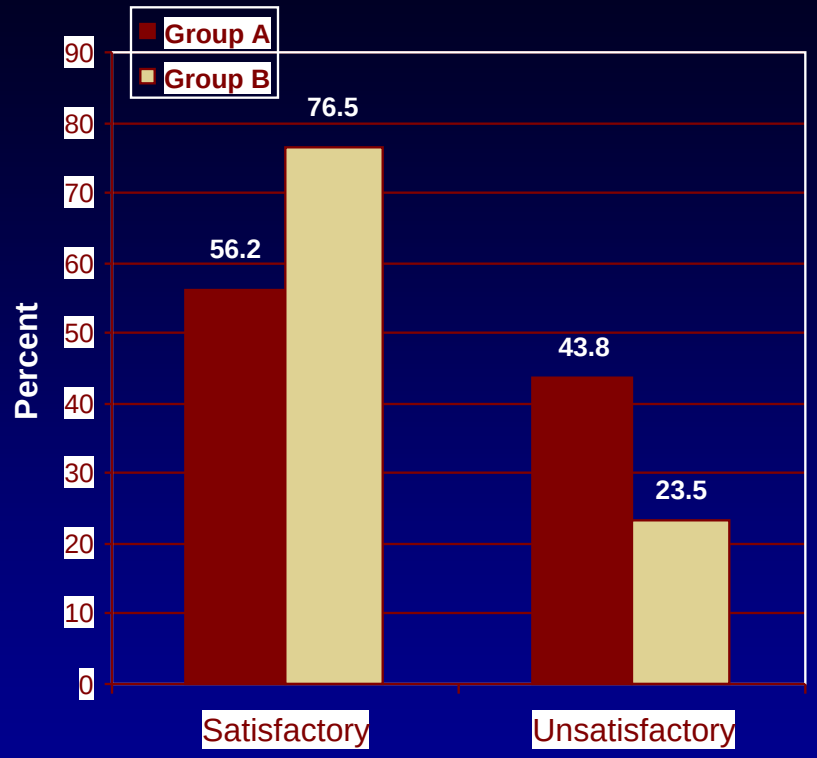
- Safety
  - Safety from direct organ toxicity is a pre-requisite
  - Safety from cancer and from repeated procedures (cost,risk) depends on efficacy
- Efficacy
  - Is the key to the primary purpose (cancer prevention) – it outranks tolerability (informed patients agree with this – and have)
- Tolerability
  - Poor tolerability is unsafe because it reduces willingness to be screened and surveyed

Bowel preparation science

- Greatest achievement of the past two decades:
  - Split-dosing adds more to efficacy than any effect of switching from one preparation to another
- Most incorrect conclusion:
  - Non-inferiority equals equivalence

Split-Dosing Provides More Satisfactory Results Than Traditional Dosing (cont)



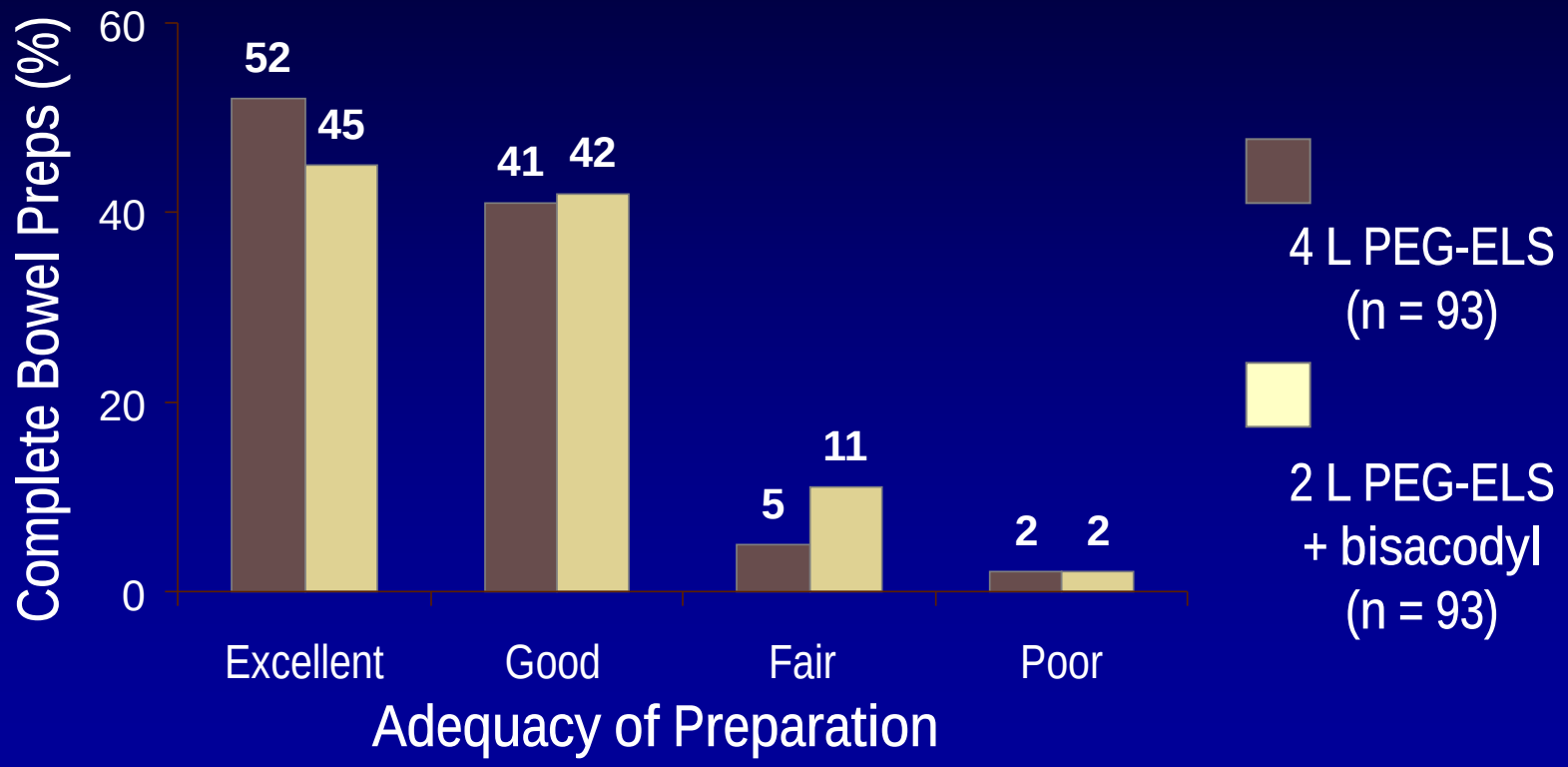


Group A = 4 L of PEG on the night before the procedure; Group B = 2 L of PEG on the evening before and 2 L on the morning of the procedure.

Reprinted from Aoun et al. *Gastrointest Endosc*. 2005;62(2):213-218.

Half-lytely
Efficacy Results

- Quality of cleansing was not significantly different between groups (*P* = 0.16)



DiPalma et al. *Am J Gastroenterol*. 2003;98(10):2187-2191.

Rates of inadequate preparation in clinical reports

- Rates of 20-40%
- References:
  - Froehlich GIE 2005;61:378-84
  - Harewood GIE 2003;58:76-9
  - Lebwohl DDS 2010;55:2014-20
  - Ness AJG 2001;96:1797-802
  - Athreya Aust NZ Surg 2011;81:261-5
  - Borg CGH 2009;7:670-5
  - Chung J Clin Gastro 2009;43:448-52
  - Hendry Colorectal Dis 2007;9:745-8

Recent changes in bowel preparation guidelines

- Split-dosing preferred
- USMSTF (ACG, ASGE, AGA) and ACG/ASGE quality task force have both adopted the following recommendation:
  - Clinicians in practice should achieve adequate rates of bowel preparation in ≥ 85% of outpatient examinations on a per physician basis
    - Consequences of 20-40% rates of inadequate preparation are too great a burden (1% rule)

Adequate vs inadequate

- MSTF operational definition: if the preparation allows identification of lesions > 5 mm in size then the preparation is ADEQUATE
  - Not a bowel preparation scale
  - Made-up operational definition based on the biology of colon polyps
- ADEQUATE for WHAT?
  - Adequate to follow the screening and surveillance intervals recommended in MSTF guidelines

Patient perspective on cleansing endpoints

- Patient should care first about the quality of the preparation after completion of intra-procedural cleansing
  - Affects the quality of mucosal inspection (effect is considerably less than the effect of the operator)
  - Affects the interval before the next examination
  - Patients will assume safety (rightly so)
  - Tolerability is very important to patients (they may NOT understand that efficacy is even more important)

The judging point

- The judging point is the point in time when the prep is graded (and adequacy determined)
- From the patient and clinicians' perspective the judging point comes after completion of the intraprocedural cleansing
  - i.e.: at the judging point patients and clinicians don't care at all about fluid or other material that was removed

Clinician perspective on cleansing endpoints

- Same as the patient's with one key difference:
- Efficiency: clinicians do not want to expend great effort to reach the judging point
  - If the work required to move marginal preps to adequate preps is excessive clinicians will abandon or modify a prep or abandon intraprocedural cleansing
  - This aspect of bowel cleansing efficacy is not captured by the clinical judging point

Intraprocedural work

- 525 patients
- Mean procedure time: 24.1 minutes
- Mean washing and suctioning time (4.1 minutes (17% of all procedural time)
- Adequacy conversion rate by intraprocedural cleaning: 90% to 96%

  - MacPhail et al GIE doi10.1016/j.gie.2014.05.002

The clinician and efficacy:

- 2 things to care about:
  - How often did we fail? (prep inadequate)
  - How much work did it take to achieve the level of adequacy?

Bowel preparation scales

- Aronchick
  - Aronchick GIE 2004; 60: 1037-8
- Ottawa
  - Rostom GIE 2004;59: 482-6
- Boston
  - Lai GIE 2009; 69: 620-25
  - Calderwood GIE; 2010; 72;686-92
- Chicago
  - Gerard; Clinical Translational Gastroenterology (2013) 4, e43; doi:10.1038/ctg.2013.16

Bowel preparation scales

Scale	Validated	Considers retained fluid	Predicts an adequate preparation
Aronchick	Yes	Yes	
Ottawa	Yes	Yes	
Boston	Yes	No	Score of ≥ 2 in each segment
Chicago “Modified Chicago”	Yes	Yes No	Score of ≥ 25 defines a preparation that allows ≥ 95% of mucosa to be seen

Boston Bowel Preparation Scale

- Right, transverse and left colon segments
  - 0 = unprepared colon segment with stool that cannot be cleared
  - 1 = portion of mucosa in segment seen after cleaning, but other areas not seen because of retained material
  - 2 = minor residual material after cleaning, but mucosa of segment generally well seen
  - 3 = entire mucosa of segment seen well after cleaning

  - Total score ranges from 0 to 9
    - Lai et al GIE 2009;69:620-25

Chicago Bowel Preparation Scale

- Cleaning scores
  - 0 = unprepared colon segment with stool that cannot be cleaned (> 15% of the mucosa not seen)
  - 5 = portion of mucosa in segment seen after cleaning; but up to 15% of the mucosa not seen
  - 10 = minor residual material after cleaning, but mucosa of the segment generally well seen
  - 11 = entire mucosa of segment well seen after washing
  - 12 = entire mucosa of segment well seen before washing (suctioning of liquid allowed)
- Fluid scale (not shown here)
  - Gerard Clin Trans Gastroenterol (2013) 4, e43;doi:10.1038/ctg.2013.16

Correlation with adequate preparation

- Boston BPS
  - Overall score ≥ 6 or score ≥ *2 in each segment* predicts doctors will follow screening and surveillance guideline
    - Calderwood GIE; 2014; 80:269-76
- Chicago BPS
  - Score of 25-36 predicts adequate preparation (≥ 95% of mucosa seen) by definition
    - Gerard Clin Trans Gastroenterol (2013) 4, e43;doi:10.1038/ctg.2013.16

Bowel preparation scales

Scale	Validated	Considers retained fluid	Predicts an adequate preparation
Aronchick	Yes	Yes	
Ottawa	Yes	Yes	
Boston	Yes	No	Score of ≥ 2 in each segment
Chicago “Modified Chicago”	Yes	Yes No	Score of ≥ 25 defines a preparation that allows ≥ 95% of mucosa to be seen

Should bowel prep studies have an ADR endpoint?

- No

What else should clinician's care about?

- Why do patients fail bowel preparation regimens?
  - Medical factors
  - Patient factors

Medical factors

- Chronic constipation
- Opioids, tricyclics
- Obesity
- Diabetes mellitus
- Previous colon resection
- Previous incomplete colonoscopy

Patient factors

- Poor health literacy
  - Medicaid insurance
  - English not first language
    - Solution: navigation
- Low patient activation
    - Possible solution: education

Endoscopists frequently don't adjust for predictors

- Use high volume aggressive preparations in all patients?
  - Patients are dissatisfied and go elsewhere
- Use low volume well-tolerated preparations in all patients?
  - Higher rates of inadequate preparation
- Why not adjust the dose for predictors?
  - Deceived by non-inferiority studies
  - Offering multiple preparations increases costs
  - Adjustment requires costly closed access or phone triage

A clinician's recommendations to the FDA

- Safety is a presumed requisite
- Discourage evening-before regimens from further testing
- Encourage testing in hard to prepare populations
- Encourage use of efficacy scales that get at endpoints relevant to patients and clinicians
  - Should reflect rates of inadequacy
  - Should reflect clinical judging point
  - Should reflect the work required to reach the judging point
- Place greater value on tolerability

Key research questions for investigators:

- What scale in clinical trials best reflects important outcomes re: efficacy?
  - Adequacy rate
  - Work to achieve adequacy
- What preparations are best tolerated? Most likely to be repeated? i.e. studies with these factors as primary endpoints
- What preparations are most effective in difficult to prepare patients?

Open Forum Q & A

Questions?

Brad Conway

American College of Gastroenterology

301.263.9000

bconway@gi.org