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Class Review: Antidiarrheals

Date of Review: January 2017

Purpose for Class Review:
To identify appropriate utilization management strategies for drugs used to treat diarrhea.

Research Questions:
1. What is the comparative efficacy and effectiveness for bismuth subsalicylate, loperamide, diphenoxylate/atropine, paregoric, crofelemer, or opium tincture in management of diarrhea?
2. What are the comparative harms or potential abuses for bismuth subsalicylate, loperamide, diphenoxylate/atropine, paregoric, crofelemer, or opium tincture?
3. Are there subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities for which one treatment for diarrhea is more effective or associated with fewer adverse events?

Conclusions:
- There is insufficient comparative evidence of efficacy and effectiveness between bismuth subsalicylate, loperamide, diphenoxylate/atropine, paregoric, crofelemer and opium tincture.
- Moderate quality evidence shows that the addition of loperamide to ciprofloxacin for treatment of traveler's diarrhea may decrease the duration of diarrhea within the first 24 to 48 hours of symptom onset.[1]
- Opium tincture has not been evaluated by the United States Food and Drug Administration (FDA) for safety and effectiveness because it was marketed before 1962.[2]
- The FDA recently published a warning about possible cardiac toxicity related to loperamide abuse or misuse at doses greater than 16 mg per day or when used with specific medications that delay loperamide metabolism.[3]
- Paregoric and diphenoxylate/atropine labeling now contain warnings regarding safety issues associated with the entire class of opioid medications.[4]
- Moderate quality evidence reveals that crofelemer is safe and effective in decreasing frequency of diarrhea in HIV-seropositive individuals stable on anti-retroviral therapy.[5]
- Low quality evidence shows that loperamide may decrease duration of diarrhea by 0.8 days as well as decrease stool frequency in children when used as an adjunct to oral or intravenous hydration.[6]

Recommendations:

- Add antidiarrheal medications to the Oregon Health Plan (OHP) fee-for-service practitioner-managed prescription drug plan.
- Designate loperamide as the preferred agent for this class. All other antidiarrheal agents will be designated as non-preferred to restrict use to only funded conditions under the OHP.
- Add quantity limits to loperamide, diphenoxylate/atropine, and crofelemer to insure safe and appropriate use:
    - Loperamide = maximum 16 mg per 24 hours
    - Diphenoxylate/atropine = maximum 20 mg/0.2 mg per 24 hours
    - Crofelemer = maximum 500 mg per 24 hours

Background:

According to the World Health Organization (WHO), there are about 2 billion cases of diarrheal disease worldwide every year.[7] In the United States (U.S.) alone, an estimated 211–375 million episodes of diarrheal illness occur each year, resulting in 73 million physician consultations, 1.8 million hospitalizations, and 3100 deaths.[8] An estimated $6 billion each year is spent on medical care and lost productivity due to foodborne diseases in the U.S., most of which cause diarrhea.[8]

Acute diarrhea is defined as the passage of loose or watery stools at least 3 times in a 24-hour period for 14 days or less.[8] Most cases of acute diarrhea in adults are infectious due to viruses, bacteria, or protozoa. Consumption of tainted food, exposure to certain animals (e.g., poultry, turtles, or reptiles), exposure to children with diarrhea (e.g., day care providers), or travel to resource-limited countries can result in infection with microbes that cause diarrhea.[8] Protracted infections caused by parasites or recurrent infections due to *Clostridium difficile* may present as persistent diarrhea that lasts greater than 2 weeks.[9] In children, the causes of acute diarrhea can be related to feeding, associated with antibiotic therapy, or due to enteric viruses.[8] Chronic diarrhea is defined as the production of loose stools with or without increased stool frequency for more than 4 weeks.[10] Chronic diarrhea is rarely caused by infectious organisms.[9] Stools that are watery, bloody or fatty require individualized diagnostic testing to differentiate between infectious diarrhea, irritable bowel syndrome (IBS), small bowel dysfunction, celiac disease, malabsorption, lactase deficiency, neoplasm, pancreatic insufficiency or laxative abuse.[11]

The epidemiology of diarrhea varies by geographic region. Developing countries with limited infrastructure have more cases of pediatric infectious diarrhea caused by *Giardia*, *Campylobacter*, *Rotavirus*, and *Cryptosporidium* due to poor sanitation practices.[9] If diarrhea is not managed in children, it can lead to severe dehydration and death. It is estimated that diarrheal illnesses are responsible for 2 to 4 million childhood deaths worldwide each year.[12] Resource-rich countries, such as the U.S., tend to have more cases of acute diarrhea caused by foodborne pathogens (e.g. *Salmonella*, *Shigella*, *Escherichia coli*).[9] In resource-rich countries, older persons have increased risk of mortality associated with chronic diarrhea.[13] If untreated, chronic diarrhea may lead to dehydration and renal failure in this population.[13]

Infectious diarrhea or colitis associated with enteric infections (e.g., food poisoning) are funded conditions under the Oregon Health Plan (OHP) on line 150 of List of Prioritized Services.[14] Disorders of stomach function and other functional digestive disorders (line 531) are not funded by OHP.[14] A complete list of ICD-10 codes associated with diarrhea and their respective OHP funding lines are included in **Table 5** of **Appendix 1**. Most categories of diarrheal illness are not funded by OHP.

This class review will focus on antidiarrheal treatment in industrialized countries such as the U.S. Depending on the etiology, management of diarrhea includes oral rehydration, electrolyte replacement, diet modification, selective antimicrobial therapy or anti-diarrheal therapy.[10] Antidiarrheal therapy is used to manage diarrhea in appropriate circumstances to reduce stool frequency and abdominal pain.[15] Antimotility agents such as loperamide, diphenoxylate/atropine, opium

tincture and paregoric increase intestinal transit time and enhance the potential for reabsorption of fluid and electrolytes.[15] The indications and dosing of these agents are outlined in **Table 1**. Bismuth salicylate is an OTC antisecretory agent aimed at reducing water and electrolyte loss secondary to prolonged diarrhea.[15] It is hydrolyzed to salicylic acid in the stomach, which helps to reduce intestinal inflammation.[16] Bismuth subsalicylate has some limitations including: frequency of administration (every 30-60 minutes, up to 8 tablets per day), delayed onset of action (up to 4 hours), interaction with the absorption of other medications such as doxycyline, and has some unpleasant adverse effects (black stool, black tongue).[15] The mechanism of action and pharmacokinetics of antidiarrheal agents are outlined in **Table 3** of **Appendix 1**.

Although opium tincture has been available for many years, it has not been reviewed by the FDA to be safe and effective.[2] The original Federal Food and Drugs Act of 1906 brought drug regulation under federal law. That Act prohibited the sale of adulterated or misbranded drugs, but did not require that drugs be approved by FDA. In 1938, Congress required that new drugs be approved for safety. In 1962, Congress amended the 1938 law to require manufacturers to show that their drug products were effective, as well as safe. As a result, all drugs approved between 1938 and 1962 had to be reviewed again for effectiveness.[17] The Drug Efficacy Study Implementation (DESI) was the process used by the FDA to evaluate effectiveness in this group of drugs.[18] For a variety of historical reasons, some drugs, mostly older products including opium tincture, continue to be marketed in the U.S. without required FDA approval.[19]

The safety and efficacy of loperamide in managing acute and chronic diarrhea at therapeutic doses has been well documented since it was first marketed in the U.S. in 1977.[20] Loperamide is an opioid agonist with relatively low gastrointestinal absorption and poor blood-brain penetration.[3] Two open label studies compared the efficacy of loperamide to bismuth subsalicylate in reducing frequency of diarrhea within 24 hours.[16, 21] The details of the two studies are summarized in **Table 2**. The first study compared loperamide 4 mg for one dose followed by 2 mg after each loose stool (max 16 mg per day) to bismuth subsalicylate 30 ml every 30 minutes for 3.5 hours over 2 days in 217 subjects.[21] Students visiting seven countries in Latin America that experienced acute, nondsyenteric traveler's diarrhea were enrolled in the study. The number of unformed stools passed per treatment period (24 vs 48 hours) was used to compare the two medications. The authors found the subjects receiving loperamide passed fewer stools compared to bismuth subsalicylate during the first 24 hours of therapy ($p < 0.002$).[21] During the next 48 hours, the loperamide group passed fewer unformed stools than bismuth ($p < 0.05$).[21] Both medications were well tolerated, although constipation was experienced by more subjects in the loperamide group compared to the bismuth group ($p < 0.25$).[21] A similar study compared loperamide 8 mg per 24 hours to bismuth subsalicylate 4.9 grams over 2 days in 203 adult students traveling to Mexico who were diagnosed as having acute, non-specific diarrhea.[16] Within the first 24 hours, the number of unformed stools decreased more in the loperamide group (n= 0.4) compared with the bismuth group (n = 0.08; p = 0.01).[16] By 48 hours the decrease in unformed stools was the same for both groups (n= 0.02, p = 0.92). However, the mean time to last unformed stool was significantly decreased with loperamide (9.9 hours) compared to bismuth subsalicylate (17.3 hours; $p < 0.004$).[16] Both treatments were well tolerated and none of the adverse effects reported resulted in discontinuation of therapy.[16] Antimotility agents are not recommended for use in infectious diarrhea without antibiotic therapy.[15] In addition, these agents should not be used as monotherapy in diarrhea accompanied by bloody stool, fever or abdominal pain.[8, 15] However, bismuth is a safe alternative to loperamide in patients with fever and inflammatory diarrhea.[15]

Diphenoxylate/atropine is approved for adults and children over the age of 2 years to reduce symptoms associated with diarrhea.[22] Atropine is added to this combination therapy to decrease abuse of diphenoxylate, which is a meperidine analog.[23] Diphenoxylate/atropine should not be used in patients with diarrhea due pseudomembranous enterocolitis or due to enterotoxin producing bacteria such as: *Shigella, Salmonella,* toxigenic *E.Coli*, *Campylobacter jejuni* or *C.difficle*.[22] There are no comparative trials of diphenoxylate/atropine with other antidiarrheal agents.

Noninfectious diarrhea in HIV-infected patients is usually secretory and caused by anti-retroviral therapy, HIV-associated enteropathy or HIV-associated malignancies, or pancreatitis.[24] All classes of anti-retrovirals can cause diarrhea; however, ritonavir-boosted protease regimens are particularly associated with

diarrhea.[24] A clinical trial review indicated up to 19% of anti-retroviral treated patients experienced drug-related diarrhea that was least moderate in intensity.[25] Most anti-diarrheal agents do not have targeted activity against the cause of secretory diarrhea and are not very effective.[24] Crofelemer inhibits intestinal luminal chloride channels, which reduces the efflux of sodium and water into the gastrointestinal (GI) lumen.[24] Crofelemer is poorly absorbed from the GI tract so systemic exposure is minimal.[24] A phase 3, randomized double-blind trial conducted in HIV-seropositive patients on anti-retroviral treatment evaluated the optimal dose, efficacy and safety of crofelemer for noninfectious diarrhea.[5] The details of this study are summarized in **Table 2**. Patients were stabilized on an anti-retroviral regimen for ≥ 4 weeks with a history of diarrhea for ≥ 1 month. This study was completed in 2 stages. The first stage randomized 196 patients with chronic diarrhea to 3 doses of crofelemer (125mg, 250mg, or 500mg) or placebo twice daily over 4 weeks. The second stage was completed in 180 new patients to compare crofelemer 125mg orally twice daily to placebo over 4 weeks. Primary efficacy analysis was the percentage of patients who achieved clinical response (2 or less watery stools per week during ≥ 2 of 4 weeks).[5] More patients receiving crofelemer 125 mg twice daily achieved clinical response versus placebo (17.6% vs 8 % p = 0.01).[5] Based on this data, the number of patients needed to treat to achieve one patient with clinical response is 10 patients. Crofelemer 125 mg twice daily resulted in a greater change from baseline in number of daily watery bowel movements (p= 0.04) and daily consistency score (p = 0.02) versus placebo.[5] Crofelemer was minimally absorbed and well tolerated with a safety profile comparable to placebo.[5] The authors concluded crofelemer provided significant improvement in diarrhea symptoms in HIV-seropositive patients taking stable anti-retroviral therapy.[5] Crofelemer has been studied in other diarrheal conditions including IBS-associated diarrhea, traveler's diarrhea, and acute infectious diarrhea and has not been found to be very effective in treating these conditions.[24] However, it is only approved by the FDA for management of diarrhea specifically associated with anti-retroviral therapy in HIV-seropositive individuals.[26] There are no head-to-head trials comparing crofelemer to other anti-diarrheal agents.

The use of antimotility agents in children less than 5 years of age has been discouraged by the WHO due to safety concerns.[27] Bismuth subsalicylate, loperamide diphenoxylate/atropine, and paregoric are the only antidiarrheal agents that are FDA approved for use in children over 2 years of age. For children under the age of 13 years, the liquid formulation of diphenoxylate/atropine is preferred to enhance appropriate dosing.[23] Pediatric dosing recommendations for antidiarrheal agents are outlined in **Table 1**.

A recent study evaluated loperamide exposures reported to the National Poison Data System to assess trends in loperamide toxicity associated with intentional misuse and abuse.[28] There was a 91% increase in reported loperamide exposures from 2010 to 2015, of which half were single-agent loperamide use only.[28] Loperamide exposures reported to the National Poison Data System increased at approximately 38 cases per year (95% confidence interval (CI) 32.5 to 42.9; P < 0.0001).[28] Fifteen deaths were reported during this time frame, of which 8 involved single-agent loperamide abuse.[28] The FDA issued a warning in June 2016 that higher than recommended doses of loperamide, including through abuse or misuse of the product, can cause serious cardiac events that can lead to death.[3] Forty eight cases of serious cardiac events associated with loperamide use have been reported to the FDA since 1976.[3] Thirty one of the cases resulted in hospitalizations and 10 patients died.[3] The most frequently reported cardiac events were syncope (n=24), cardiac arrest (n=13), QT interval prolongation (n=13), ventricular tachycardia (n=10), and Torsades de Pointes (n=7).[3] The risk of these cardiac events, including abnormal heart rhythms, was increased when high doses of loperamide were taken with other medications that interact with loperamide.[3] Drugs that interact with loperamide include: cimetidine, clarithromycin, erythromycin, gemfibrozil, itraconazole, ketoconazole, quinidine, ranitidine and ritonavir. The majority of reported cardiac events occurred in individuals intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria.[3] In cases of abuse, patients have often combined loperamide with other drugs that inhibit its metabolism or increase its absorption in order to enhance the euphoric effects of loperamide.[3]

The FDA issued warning in March 2016 about safety issues associated with the entire class of opioid medications including diphenoxylate/atropine and paregoric.[4] These risks include: potentially harmful interactions with numerous other medications, leading to serotonin syndrome; problems in which the

adrenal glands do not produce adequate amounts of cortisol; and decreased sex hormone levels, possibly leading to reduced interest in sex, impotence, or infertility.[4] The FDA is requiring class-wide safety labeling changes for all opioid pain medications warning of these risks.[4] A summary of warnings and precautions for all antidiarrheal agents is outlined in **Table 4** of **Appendix 1**.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Indications and Dosing.[23]

Antidiarrheal Drug	**Indication(s)**	**Strength** (all routes oral)	**Pediatric Dose/Frequency**	**Adult Dose/Frequency**
Loperamide (Imodium®)	• Acute diarrhea • Chronic diarrhea • Traveler's diarrhea • High output ileostomy	2 mg tablet 2 mg capsule 1 mg/7.5 mL suspension	Age: 2-5 years (13-20 kg): 1 mg TID Age: 6-8 years (20-30 kg): 2 mg BID Age: 8-11 years (>30 kg): 2 mg TID Age ≥12 years: see adult dosing	Age ≥ 12 years: 4 mg followed by 2 mg after each loose stool (max 16 mg/day)
Bismuth-subsalicylate (Pepto-Bismol®)	• Diarrhea • *H. pylori* infection	525 mg/15 mL suspension 262 mg tablet	Age <12 years: not recommended	524 mg every 0.5 to 1 hour PRN (max 8 doses or 4192 mg per day) *H. pylori* dosing is 525 mg po QID for 10-14 days as part of a multi-drug regimen
Diphenoxylate/Atropine (Lomotil®)	• Diarrhea	2.5 mg/0.025 mg/5 mL solution 2.5 mg/0.025 mg tablet	Age: ≥2 years: 0.3-0.4 mg/kg/day *oral solution* divided QID (max 20 mg diphenoxylate per day)	2 tablets or 10 mL solution QID until control achieved (max 20 mg of diphenoxylate per day (40 mL or 8 tablets)
Opium Tincture	• Diarrhea	10 mg/mL tincture	Safety and efficacy not established in children	6 mg QID
Paregoric	• Diarrhea	2 mg/5 mL solution	0.1 – 0.2 mg/kg daily to QID	5 -10 mL daily to QID
Crofelemer (Mytesi®)	• Non-infectious diarrhea in HIV+ adults on stable antiretroviral therapy	125 mg delayed-release tablets	Safety and effectiveness not established	125 mg BID

Abbreviations: BID = twice daily; kg = kilograms; mg = milligrams; mL = milliliters; PRN = as needed; QID = four times daily

Table 2. Summary of Pivotal Studies Completed.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr>
<td>Johnson PC et al[21]

OL RCT</td>
<td>Loperamide 4 mg followed by 2 mg after each stool (max 16 mg per day) over 2 days

Vs.

Bismuth Subsalicylate 30 mL every 30 min for 3.5 hours over 2 days (7 doses or 210 mL total)</td>
<td>Students visiting 7 Latin American countries

Treatment of acute nondsyenteric traveler’s diarrhea

N = 217</td>
<td>Improvement (decrease in diarrhea severity) defined as: decrease by half of the number of unformed stools compared to the previous 24 hours

Or

Disappearance (total relief) of diarrhea</td>
<td>Percent with Improvement and Relief in Diarrhea within 24 hours

Loperamide 72/111 (64%)

Bismuth 45/107 (42%)

Loperamide favored over bismuth (p<0.03 for relief and p<0.0001 for improvement)</td>
</tr>
<tr>
<td>DuPont HL et al[16]

OL PG RCT</td>
<td>Loperamide 4 mg followed by 2 mg after each unformed stool (max 8 mg per day)

Vs.

Bismuth 612.5 mg (35 mL) every 30 minutes as needed up to 4.9 grams per 24 hours (8 doses maximum)</td>
<td>Adult students from US or Latin America with acute diarrhea

N = 203</td>
<td>Number of unformed stools passed

And

Time elapsed from start of therapy to occurrence of last unformed stool</td>
<td>Average Number of Unformed Stools per 12 hour period after initiation of therapy
<table>
<tr><th>Period</th><th>Loperamide</th><th>Bismuth Salicylate</th><th>p-value*</th></tr>
<tr><td>1 – 12 hours</td><td>0.9</td><td>2.3</td><td>0.0001</td></tr>
<tr><td>2 – 24 hours</td><td>0.4</td><td>0.8</td><td>0.01</td></tr>
<tr><td>3 – 36 hours</td><td>0.3</td><td>0.6</td><td>0.17</td></tr>
<tr><td>4 – 48 hours</td><td>0.2</td><td>0.2</td><td>0.92</td></tr>
</table>
Time to last unformed stool (mean time)
Loperamide: 9.9 hours
Bismuth subsalicylate: 17.3 hours
p<0.004</td>
</tr>
<tr>
<td>Macarthur RD et al[5]

PC DB RCT
Phase 3

4 weeks</td>
<td><u>Stage 1:</u>
Crofelemer 125 mg, 250 mg, or 500 mg po BID
Vs.
Placebo

<u>Stage 2:</u>
Crofelemer 125 mg po BID
Vs.
Placebo</td>
<td>HIV sero-positive patients with chronic diarrhea (≥ 1 month) on antiretroviral therapy ≥ 1 month

Stage 1 (dose finding 125mg, 250mg, or 500mg BID)
N = 196

Stage 2: (crofelemer 125mg BID vs placebo)
N = 180</td>
<td>Percent of patents who achieved clinical response (decrease in watery stools).</td>
<td>Stage 2 results: Patients with clinical response (defined as ≤ 2 watery stools per week during ≥2 of 4 weeks)
<table>
<tr><th>Crofelemer 125 mg po BID (n=136)</th><th>Placebo (n=138)</th><th>Treatment Difference</th><th>p-value</th></tr>
<tr><td>24/136 (17.6%)</td><td>11/138 (8.0%)</td><td>9.6%</td><td>0.0096</td></tr>
</table>
</td>
</tr>
</table>

Abbreviations: BID = twice daily; OL = open label; PC = placebo-controlled; PG = parallel group; po = orally; RCT = randomized controlled trial

Methods:
A Medline literature search for systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Conducting clinical trials for the treatment of diarrhea is difficult due to the different causes of diarrhea, varying definitions of diarrhea based on frequency and duration of unformed stools, and different patient populations(from children to the elderly).[20] Consequently, there is insufficient evidence to guide the use of antidiarrheal agents as there are very few head-to-head trials. However, 2 systematic reviews were identified and assessed for this review.

Systematic Reviews:
Adjunctive Loperamide with Antibiotics for Traveler's Diarrhea
A Cochrane Collaboration review established an effective advantage of antibiotic therapy, compared with placebo, for treatment of traveler's diarrhea.[29] This systematic review evaluated the effect of loperamide in conjunction with antibiotic therapy in adults on treatment outcomes.[1] Clinical trials that studied treatment of adults with infectious traveler's diarrhea in which an adjunctive antimotility agent was used were eligible to be included in the review. Nine studies published during 1990-2007 consisting of 12 different antibiotic regimens with adjunctive loperamide met inclusion criteria to be included for analysis.[1] The average size of the treatment arms was 60 patients; the smallest involved 43 patients, the largest involved 106 patients, and all were randomized, double-blind, placebo-controlled trials, except 2, which were randomized, evaluator-blind clinical trials.[1] Six studies evaluated U.S. student travelers to Mexico. The other 3 studies included U.S. military personnel in Egypt, Thailand, and Turkey. The mean age of the study populations was 24 years (9 studies; age range, 23–27 years), and patients presented a mean of 36 h (n=7 studies; range, 23–48 h) after symptom onset, with a median of 6 stools in the previous 24 h (n=7 studies; range, 2.3–7).[1] The authors found the studies to be of moderate quality.[1] Among 6 paired studies comparing antibiotics alone versus antibiotics in combination with loperamide, the odds of clinical cure at 24 hours and 48 hours favored combination therapy (odds ratios [OR] 2.6 (95% CI, 1.8-3.6) and OR 2.2 (95% CI, 1.5-3.1), respectively).[1]. Most of the studies independently demonstrated that combination regimens offer an advantage of antibiotic alone regimens for clinical cure at the first 24–48 h. By 72 hours, the addition of loperamide did not appear to offer any significant advantage to antibiotic treatment alone.[1] Time to last unformed stool (TLUS) after initiation of therapy was also evaluated. Five of 6 studies had extractable information on this outcome; although all demonstrated negative mean TLUS durations (meaning that adjunctive therapy decreased the time after treatment to last diarrheal stool, compared with antibiotics treatment alone) of 2–23 h, there was considerable heterogeneity among the studies (P<.001)[1] When estimates of TLUS among studies with evaluable loperamide antibiotic combination regimens were pooled (10 studies) using a random-effects model, it was estimated that TLUS for these combination treatment regimens was 17 h (95% CI, 9–24 h).[1] The most common adverse effect of loperamide was constipation, which was rarely reported.[1] There was moderate evidence that antibiotic therapy with adjunctive loperamide offers an advantage over antibiotics alone by decreasing the duration of illness and increasing the probability of early clinical cure in adult patients with travelers' diarrhea.[1]

Loperamide in Children

A systematic review and meta-analysis was conducted in children to evaluate the safety and efficacy of loperamide compared to placebo.[6] Thirteen studies met inclusion criteria established by the reviewers. Four study design aspects were evaluated: allocation of concealment, generation of allocation sequence, blinding and inclusion of all randomized participants. The authors categorized the 4 study design characteristics as adequate, not adequate or unclear. Most of the studies did not meet the requirements for adequate methodological quality and only 4 studies provided outcome data that could be combined.[6] The primary outcomes of interest were the characteristics of the clinical course of diarrhea and the incidence of adverse effects. [6] Compared with patients who received placebo, patients allocated to loperamide were less likely to continue to have diarrhea at 24 hours (prevalence ratio 0.66, 95% CI: 0.57 to 0.78), had a shorter duration of diarrhea by 0.8 days (95% CI: 0.7 to 0.9 days), and had a lower count of stools at 24 hours (0.84, 95% CI: 0.77 to 0.92).[6] Serious adverse events, defined as ileus, lethargy, or death, were reported in eight out of 927 children allocated to loperamide (0.9%, 95% CI: 0.4% to 1.7%).[6] Serious adverse events were not reported in any of the 764 children allocated to placebo (0%, 95% CI: 0% to 0.5%).[6] Low quality evidence shows that loperamide appears to decrease diarrhea duration and frequency in children when used as an adjunct to oral or intravenous hydration.[6] Limitations of this systematic review included a lack of consistency in outcome measures and very few well designed studies that could be included in the meta-analysis.

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Appendix 1: Specific Drug Information

Table 3. Clinical Pharmacology and Pharmacokinetics.[23,30]

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics
Loperamide (Imodium®)	Inhibit peristalsis Antisecretory	Bioavailability 0.3% (poor)	Renal Excretion 1% Fecal Excretion 25-40%	Half-life: 7-15 hours
Bismuth-subsalicylate (Pepto-Bismol®)	Undetermined	Bismuth subsalicylate: Hydrolyzed in GI tract to bismuth and salicylic acid Bismuth: <1% absorbed from GI tract into systemic circulation Salicylic acid: >80% absorbed following oral administration	Salicylic acid: Extensively metabolized Bismuth: Excreted principally via urine and biliary routes. Salicylic acid: About 10% excreted unchanged in urine	Half-life: 5-11 days Cmax: 40 mcg/L (tablet) Vd: 170 mL/kg (salicylic acid)
Diphenoxylate/Atropine (Lomotil®)	Slows intestinal motility (diphenoxylate) *Sub-therapeutic doses of atropine are added to discourage abuse	Bioavailability >90% (good)	Metabolism: Hepatic to active metabolite: diphenoxylic acid Excretion: Renal 14%; fecal: 49%	Half-life: 2.5 hours (diphenoxylate) Cmax: 163 mg/mL Vd: 324 L
Opium Tincture	Slows intestinal motility	Variable	Hepatic: Conjugation Renal: 75%	N/A
Paregoric	Slows intestinal motility	Variable	Hepatic: Conjugation Renal: 75%	N/A
Crofelemer (Mytesi®)	Inhibits chloride ion channels that regulate chloride ion and fluid secretion by intestinal epithelial cells, resulting in blockade of chloride ion secretion and the associate water loss associated with diarrhea	Minimal	No metabolites have been identified Elimination route has not been identified in humans due to minimal systemic absorption	N/A

Abbreviations: Cmax = maximal concentration in blood; GI = gastrointestinal; Vd = volume of distribution

Use in Specific Populations:
Loperamide: Loperamide is contraindicated in pediatric patients <2 years of age.[30]

Bismuth subsalicylate: Do not use bismuth subsalicylate in children or adolescents who have or are recovering from varicella or influenza-like symptoms.[30] Changes in behavior accompanied by nausea and vomiting in children or adolescents taking the drug may be an early sign of Reye's syndrome.[30]

Diphenoxylate/atropine: Use with caution in children; not recommended for use in children <2 years of age.[30] Younger children may be predisposed to delayed toxicity; signs of atropinism may occur even at recommended doses, especially in patients with Down syndrome.[30]

Opium tincture: Not recommended for use in children.[2]

Drug Safety: Black Boxed Warnings:
Loperamide: Cases of torsades de pointes, cardiac arrest, and death have been reported with the use of a higher than recommended dosage of loperamide. [30] Avoid dosages higher than recommended in adults and pediatric patients ≥2 years due to the risk of serious cardiac adverse reactions.[30]

Opium Tincture/Paregoric: Potential for error: Do not confuse paregoric with opium tincture which is 25-times more potent.[30]

Table 4. Summary of Warnings and Precautions.[30]

Warning/Precaution	Loperamide	Bismuth	Diphenoxylate/Atropine	Opium Tincture	Paregoric	Crofelemer
CNS Effects (Drowsiness/Dizziness)	X		x	X	X	
Constipation	X					
Cardiac Arrest	X					
Reye's Syndrome		X				
Tongue Discoloration		X				
Use with Caution in Hepatic Impairment			X	X	X	
Uses with Caution in Renal Impairment			X		X	
Hypotension				X	X	
Flatulence/Nausea						X

Table 5. ICD-10 Codes Associated with Diarrhea and Associated OHP Funding.[14]

Diagnosis	ICD-10 Code	OHP Funding Line	Funding Status
Enteric Infection/Food Poisoning	A09	150	Funded
Non-infective gastroenteritis and colitis	K52.9	555	Not Funded
Irritable bowel syndrome with diarrhea	K58.0	531	Not Funded
Functional diarrhea	K59.1	531	Not Funded
Non-infective neonatal diarrhea	P78.3	531	Not Funded

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1946 to November Week 4 2016

1. Bismuth subsalicylate.mp 505
2. exp Diphenoxylate/ 364
3. lomotil.mp. 105
4. exp Loperamide/ 1550
5. exp Opium/ 2918
6. paregoric.mp. 54
7. crofelemer.mp 23
8. 1 or 2 or 3 or 4 or 5 or 6 52332
9. limit 7 to (full text and humans and (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 107
10. diarrhea {No Related Terms} 87681
11. 8 and 9 101