Antibiotic use in long-term care is very common and ensuring appropriate use of such continues to be a focus across the entire healthcare system. Per CDC data, antibiotics are among the most frequently used medications in long-term care facilities, with up to 70% of residents receiving at least one course of systemic antibiotics in a year. Studies have shown that more than one third of patients who receive an antibiotic will develop antibiotic-associated diarrhea. Diarrhea is a common side effect of antibiotics, and can occur anywhere between 5-39% of patients, depending on the type of antibiotic and patient. Older adults typically are more likely to experience diarrhea with antibiotic use than other populations. The median onset of diarrhea is 5-9 days, although it can occur as late as 2-3 weeks after discontinuing antibiotics. Cephalosporins, clindamycin, and broad spectrum penicillins have been associated with higher rates of antibiotic-associated diarrhea. In addition to being extremely unpleasant, diarrhea can contribute to patients discontinuing their antibiotics earlier than intended, which may cause difficulty in treating the infection and possibly increase the potential for resistance.

When the normal intestinal bacteria is disrupted by antibiotics, it can cause the protective barrier normally provided by the microflora to become ineffective. This can cause the gut to be unable to resist colonization by opportunistic pathogens such as *C. Difficile, Salmonella,* and *Staphylococcus aureus*. In addition, some antibiotics such as erythromycin or amoxicillin/clavulanate can increase gut motility and worsen diarrhea. Older adults are more susceptible to developing diarrhea, as the total numbers and species of normal gut bacteria decrease with age.

In an effort to reduce such adverse effects, significant time and resources should be focused on controlling antibiotic use. In addition to focusing on stewardship, one potential method of reducing adverse events such as antibiotic-associated diarrhea is to consider using probiotic bacteria.

**Probiotics**

Probiotics are live microorganisms that are considered “good” or “friendly” bacteria. They help replenish the natural GI flora with non-pathogenic bacteria. Researchers have proposed that probiotics may competitively inhibit the growth of pathogenic bacteria. The exact mechanism of action is still unknown, and likely may vary between the different species of bacteria. Probiotics can be found in dietary sources, including some yogurts or cheese, sauerkraut, and kimchi. In addition to dietary sources, probiotics are also available as oral supplements. The most common bacteria found within supplements are *Lactobacillus, Bifidobacteria, Saccharomyces boulardii,* and *Bacillus coagulans*. Probiotics are not regulated by the FDA in the way that standard medicines are—so there may be variations in what is contained in different supplements. Despite their frequent use, there remain some questions over how effective probiotics are in preventing and treating antibiotic-associated diarrhea, including *C. difficile*—associated diarrhea.
# NEW DRUGS of 2018

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Indication</th>
<th>Dosage &amp; Administration</th>
<th>Side Effects</th>
<th>Important Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andexxa®</td>
<td>Coagulation factor Xa (recombinant) inactivated</td>
<td>Antidote indicated for the treatment with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding</td>
<td>There are 2 dosing regimens given as an IV infusion in a hospital setting</td>
<td>UTIs and pneumonia</td>
<td></td>
</tr>
<tr>
<td>Firvanq®</td>
<td>Vancomycin oral solution C. diff associated diarrhea; enterocolitis caused <em>Staphylococcal aureus</em> including MRSA</td>
<td></td>
<td></td>
<td>Nausea, abdominal pain, hypokalemia</td>
<td>Available as 25mg/ml and 50mg/ml; store refrigerated before reconstituted and after; good for up to 14 days; Warning: oral vancomycin is not effective for treatment of other types of infections</td>
</tr>
<tr>
<td>Lokelma®</td>
<td>Sodium zirconium cyclosilicate</td>
<td>Treatment of Hyperkalemia (non-emergent)</td>
<td>Oral suspension; The starting dose is 10mg administered three times daily for up to 48 hours with a maintenance dose of 10mg/day</td>
<td>Edema</td>
<td>NOT indicated for emergency use; Edema is due to each 5g dose containing 400mg of sodium. Cost is $700 for 30 packets of 10mg</td>
</tr>
<tr>
<td>Ozempic®</td>
<td>Semaglutide</td>
<td>Type 2 DM</td>
<td>Once Weekly injection with or without food, same day each week Available as 0.5mg and 1mg prefilled pens</td>
<td>N/V/D, abdominal pain, constipation</td>
<td>GLP-1 receptor agonist; Cost is around $720 for a carton of 2 pens</td>
</tr>
<tr>
<td>Perseris®</td>
<td>Risperidone</td>
<td>Schizophrenia in adults</td>
<td>Once monthly SQ injection in the abdomen 90mg or 120mg dose; store in the refrigerator prior to use and bring to room temp at least 15 min prior to administration; must be reconstituted</td>
<td>Weight gain, sedation, musculoskeletal pain and injection site reactions</td>
<td>Patients will develop a lump at injection site which could last for weeks. Do not rub or massage site at any time; patients are recommended to be on at least 3mg/day of oral risperidone before use; carries the same black box warning as drugs in its class.</td>
</tr>
<tr>
<td>Repatha®</td>
<td>Evolocumab</td>
<td>Prevent heart attacks, strokes and coronary revascularization in adults with established CV disease</td>
<td>Available as prefilled syringe; single-use SureClick® autoinjector given every 2 weeks or Pushtronex® system that is a single-use on-body infusor with prefilled cartridge</td>
<td>Diabetes mellitus, nasopharyngitis, upper respiratory tract infection</td>
<td>Human monoclonal antibody that inhibits PCSK9 which in turn increases the number of LDL receptors available to clear LDL from the blood, thus lowering LDL levels; cost $1250 for 2 SureClick pens or 2 prefilled syringes or 1 cartridge; store in refrigerator until use but is stable in original box for up to 30 days</td>
</tr>
<tr>
<td>Rhopressa®</td>
<td>Netarsudil</td>
<td>Open-angle glaucoma or ocular hypertension</td>
<td>Once daily drop to affected eye</td>
<td>Eye burning or stinging, red eyes, watery eyes</td>
<td>Refrigerate until opened, then store at room temperature or may refrigerate for up to 6 weeks; Cost is around $260 for 1 vial</td>
</tr>
<tr>
<td>Drug</td>
<td>Generic</td>
<td>Indication</td>
<td>Dosage &amp; Administration</td>
<td>Side Effects</td>
<td>Important Information</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td>------------------------------------------------------</td>
<td>------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Steglatro®</td>
<td>Ertugliflozin</td>
<td>Type 2 DM</td>
<td>Once daily in the morning with or without food; 5mg and 15mg tablets</td>
<td>Female mycotic genital infections</td>
<td>SGLT2 inhibitor; Contraindicated in severe renal impairment and Dialysis; studied in use with other DM drugs; Do not start use if CrCl is &lt;60ml/min; if already on drug, stop when CrCl is between 30-60ml/min; Cost is around $300 per month</td>
</tr>
<tr>
<td>Shingrix®</td>
<td>Zoster vaccine recombinant; adjuvanted</td>
<td>Prevention of shingles in adults age &gt;50</td>
<td>Given in 2 separate doses 2-6 months apart</td>
<td>Injection site reactions, muscle pain, fatigue, HA, fever</td>
<td>IM not SQ; dead virus so can be given to immunocompromised patients; 90%+ efficacy in all age groups; Cost is around $150 per dose</td>
</tr>
<tr>
<td>Sublocade®</td>
<td>Buprenorphine</td>
<td>Moderate to severe opioid use disorder in adults who have initiated treatment with a transmucosal product</td>
<td>Monthly injection by a healthcare provider</td>
<td>Constipation, N/V, HA, drowsiness, injection site pain, itching at the injection site and abnormal liver enzymes</td>
<td>Patients need to be stable on oral regimen for at least 7 days before use. Boxed warning for risk of IV administration (vs SQ) which could result in a solid mass that could cause occlusion tissue damage or embolus; REMS drug</td>
</tr>
<tr>
<td>Vraylar®</td>
<td>Cariprazine</td>
<td>Antipsychotic for acute and maintenance tx of adults with schizophrenia and acute tx of manic or mixed episodes of bipolar I disorder</td>
<td>Once daily dose with recommended dosing range of 3-6mg/day for acute treatment; maintenance treatment is 1.5-6mg/day</td>
<td>EPS, agitation, N/V, sedation, restlessness, weight gain, constipation, blurred vision</td>
<td>8 times higher affinity for dopamine 3 receptors than dopamine 2 receptors; also acts as an agonist at certain serotonin receptors; no real affinity for cholinergic or muscarinic receptors; Cost around $1150 for 30 capsules</td>
</tr>
<tr>
<td>Xerava®</td>
<td>Eravacycline</td>
<td>Tetracycline antibiotic for the treatment of complicated intra-abdominal infections</td>
<td>IV infusion 1mg/kg over 60 min every 12 hours for 4-14 days; must be reconstituted prior to use</td>
<td>Hypotension, N/V/D, infusion site reactions</td>
<td>Increase the dose to 1.5mg/kg every 12 hours when used with strong CYP3A4 inducers; patients on anticoagulants may require a dose reduction of their anticoag dose</td>
</tr>
<tr>
<td>Zemdri®</td>
<td>Plazomicin</td>
<td>Aminoglycoside antibacterial for the treatment of complicated UTIs, including pyelonephritis caused by certain strains of bacteria in patients with limited treatment options</td>
<td>IV infusion given once daily CrCl ( \geq ) 60-&lt;90 ml/min: 15 mg/kg every 24 hours; CrCl ( \geq ) 30-&lt;60 ml/min: 10 mg/kg every 24 hours; CrCl ( \geq ) 15-&lt; 30 10 mg/kg every 48 hours Duration of treatment is 4-7 days</td>
<td>N/V/D, HTN, HA, hypotension</td>
<td>Designed to work against ESBL and CRE producing bacteria; boxed warning about the risk of ototoxicity, nephrotoxicity, neuromuscular blockade and fetal harm; Nephrotoxicity greater in elderly, impaired renal function and those on other nephrotoxic agents; monitor CrCl before, during, and after therapy; serum drug level is recommended if CrCl &lt;90ml/min Available as 500mg vial when reconstituted= 50mg/ml</td>
</tr>
</tbody>
</table>

Submitted by Bobbie Hall, Pharm D, BCGP
Consultant Pharmacist, NMG
Probiotic Use with Antibiotics…………………………………continued from page 1

**Antibiotic-Associated Diarrhea**

Limited studies have shown that probiotics appear to be effective in preventing antibiotic-associated diarrhea. One study in 2007 examined the efficacy of a probiotic drink containing *Lactobacillus* for the prevention of any diarrhea associated with antibiotic use and that caused by *Clostridium difficile*. The study looked at 135 hospital patients (with the mean age of 74) who were receiving antibiotics. The patients received the probiotic drink twice daily during a course of antibiotics, and for one week after the antibiotics were completed. The researchers found that the probiotic drink significantly reduced antibiotic-associated diarrhea (12% vs. 34%), as well as reduced the incidence of *C. Difficile* associated diarrhea.

Another study in 2010 looked at a combination probiotic that contained two strains of *Lactobacillus*. It found that patients who received a higher dose of probiotic for the duration of their antibiotic regimen (and for 5 days afterwards) had significantly fewer cases of antibiotic-associated diarrhea (15.5 vs. 44.1%). In addition, it also showed a reduction in the development of *C. difficile*-associated diarrhea.

Several meta-analyses looking at studies similar to these have shown that probiotics significantly decrease the incidence of antibiotic-associated diarrhea. Of note, the analyses found that the effects of probiotics were similar for several different formulations and durations. The most commonly used probiotics studied were *S. boulardii*, *Lactobacillus* species.

**Clostridium difficile-associated diarrhea**

*C. Difficile* is an opportunistic bacteria that colonizes in the gut after the normal gastrointestinal flora is disrupted, typically following antibiotic therapy. Unfortunately, the evidence supporting probiotic use for *C. Difficile* prevention is weaker, as there have been fewer studies done.

A Cochrane review published in 2017 examined probiotic use in preventing *C. Difficile* associated diarrhea. The researchers examined 39 randomized trials investigating the effectiveness of probiotics for preventing *C. Difficile*-associated diarrhea among patients taking antibiotics. The researchers found that when probiotics are given with antibiotics, the risk of developing *C. Difficile*-associated diarrhea is reduced by 60% on average. Trials that looked at participants at high risk demonstrated a greater benefit, with a 70% risk reduction. The authors concluded that the short-term use of probiotics appears to be safe and effective when used with antibiotics (in patients not immunocompromised or debilitated).

The Infectious Diseases Society of America noted in their *Clostridium Difficile* practice guideline published in 2018 that there is insufficient data to recommend administration of probiotics for prevention of *C. Difficile* infection. They noted that several meta-analyses have shown that probiotics may be effective for patients receiving antibiotics. However, given that the studies included a variety of different probiotic formulations and different durations of probiotic administration, there was not sufficient data to be able to recommend routine administration of probiotics. They also expressed concern over the potential for probiotic formulations to cause infections in hospitalized patients.

Of note, while the data for prevention of *C. Difficile* associated diarrhea appears inconclusive at this time, there is some limited data that suggests probiotics may be a useful adjunctive therapy to antimicrobial therapy for patients with non-severe recurrent *C. Difficile* infections.

**Choice of Probiotic Agent**

For prevention in antibiotic-associated diarrhea, most of the studies used combinations of the *Lactobacillus* species or *S. boulardii*. While no standard dose has been determined, it appears most trials used doses ranging from $10^7$ to $10^{10}$ colon-forming units (CFUs) per dose, taken 1-3 times daily. The probiotic should be continued at least as long as the patient continues to take antibiotics, and possibly up to 1 week after discontinuing the antibiotic.

**Safety**

Probiotics are generally considered safe and well-tolerated, with only mild gastrointestinal adverse effects. However, there have been rare reports of bacterial sepsis, fungemia, and endocarditis associated with probiotic use, especially in immunosuppressed patients. It has been suggested that the presence of a central venous catheter, impaired intestinal barrier, and cardiac valve disease may increase the risk of infection.

**Can I just eat yogurt?**

Bacteria have been used in food fermentation for centuries-including foods such as yogurt, sauerkraut, and kimchi. While many yogurts contain live-active *lactobacillus* cultures, most are not technically considered to be probiotics. Probiotics are typically considered as having an adequate number of microorganisms that have been shown to be beneficial to health, so most yogurts do not meet that definition. However some yogurts fortified with an adequate number of viable bacteria are classified as probiotics.

**Conclusions**

Current evidence supports using probiotics for preventing antibiotic-associated diarrhea in most patients, especially those receiving broad spectrum antibiotics. More research is required to determine the benefit of using probiotics for prevention of *C. Difficile*-associated diarrhea.
Don’t Burn Out! Self Care for the Caregiver

All too often, as the nature of a caregiver, one’s altruism clouds the ability to take pause for self-care. The ability to reflect & rejuvenate is vital for sustaining such a demanding and virtuous role and to avoid or overcome the potential pitfalls of job-related burnout. It’s important for both individuals and organizations to recognize the signs and symptoms of burnout so a “prescriptive” plan can be implemented ASAP! Why? Un-addressed burnout can lead to the following:

- High staff turnover
- Poor client satisfaction with increased complaints
- Decreased quality of service(s)
- Less than desirable work environment
- Increased potential for litigation

According to Dr. Burnout, “If you are burned out in your job, in a relationship, or in living, there are warning signs and symptoms everyone should know. If you don’t know the symptoms of burnout, you may mistake them for something else” (i.e. ambivalence, anxiety, stress, depression, irritability, relationship/financial problems, personality/character defects, etc.). “This can lead to a delay in addressing the underlying issues and needlessly prolong your suffering.”

The 3 hallmarks of burnout:

1) Emotional exhaustion
2) Depersonalization
3) Lack of a sense of personal accomplishment

*Note: All or a combination of the above are ALWAYS present in a person once they have reached job burn out.

One might be inclined to suggest it’s the individual who is responsible for burning themselves out. However, 9 out of 10 times it’s actually the work environment that has led to employee burnout. Place a highly motivated, driven, dedicated caregiver in the wrong or a toxic workplace… and boom… burn out is many more times likely to rear its ugly head.

Dr. Burnout’s 21 Symptoms of Job Burnout:

- Feeling more and more time pressured at work.
- A sense of dread associated with going to work.
- A sense of relief that the weekend has finally arrived.
- A lack of recognition or not feeling rewarded for good work.
- Feeling that job demands are unclear or unreasonable.
- Either work is no longer challenging or it has become overwhelmingly challenging.
- Work seems chaotic or too high pressured.
- A sense there is no time you can take off from work without consequences.
- Feeling that you have to be too many things for far too many people.
- Feeling as though you have no help.
- Feeling as though you no longer make a difference.
- Difficulty or inability to concentrate.
- You lack close and supportive relationships in both your work and personal life.
- More irritable, intolerant, exhausted and cynical.
- Feeling disengaged, unmotivated, uninterested or uninteresting.
- Feeling as though life is no longer worth living.
- A feeling you should be doing something else.
- A feeling you do not fit in your profession or current relationship, or they do not fit you.
- Feeling as though you have nothing left to give.
- Continuously questioning yourself, “Is this all there is to life? Is there nothing more?”

This list is not meant to stir up angst like a direct to consumer TV advertisement. Instead, it is meant to serve as a beacon of light to help identify and address the root underlying causes that perpetuate these symptoms and ultimately to come up with a plan to mitigate them.

Self-Care Suggestions:

- Read or listen to an audio book
- Regular exercise
- Aromatherapy
- Massage
- Stretch regularly
- Acupuncture
- Behavioral therapy
- Resilience Training
- Adequate sleep
- Take a vacation or staycation
- Eat mindfully & healthfully
- Institute breathing & meditative practices (Check out a free app like Headspace)
- Schedule an annual wellness visit
- Medication compliance
- Set S.M.A.R.T. personal & professional goals

Check out Dr. Burnout’s website for more information at http://www.clarkgaither.com

Article by Keely Ray, PharmD, BCGP, FASSP
Consultant Pharmacist, NMG
Opioid-Induced Constipation

Constipation is a common complaint in the elderly population due to a variety of factors, including diet, physical inactivity, natural decline in bowel function, and medication burden. It is estimated that the prevalence of constipation in older adults ranges from 25-50%, with roughly 75% of nursing home residents requiring daily laxative therapy. One of the most common causes of constipation in the elderly is the administration of medications that delay gastrointestinal transit time. Several medications used to treat issues like hypertension, anemia, depression, and chronic pain have been shown to cause constipation. Opioids are a class of medications used to treat chronic pain that carry the greatest risk of inducing constipation.

Pathophysiology

In the same way that opioids relieve pain throughout the body, these agents also produce adverse effects in various organ systems. The gastrointestinal tract is one of the main sites of opioid activity throughout the body, producing common side effects like nausea, vomiting, and constipation. Opioids induce constipation by prolonging intestinal transit time, decreasing intestinal secretions, and producing spastic intestinal contractions that do not propel bowel contents forward. These agents also increase anal sphincter tone and impair reflex relaxation, resulting in an impaired ability to evacuate the bowel. These effects can be seen even at low doses and at any time after initiating opioid therapy. Furthermore, dosage form should be considered when evaluating therapy. Orally administered opioids tend to produce greater inhibitory effects on the GI tract than IV or IM formulations.

Tolerance also plays a role in opioid-induced constipation. While it is common for patients to develop a tolerance to the analgesic effects of opioids, the rate of tolerance to gastrointestinal effects varies based on the location within the gastrointestinal tract. For example, nausea and vomiting commonly dissipate shortly after starting opioid therapy, while constipation persists. This is because tolerance to opioid activity occurs in all sections of the GI tract except for the colon. So, as higher doses are required to combat analgesic tolerance and treat pain appropriately, the constipation-inducing effect of opioids can worsen.

Clinical Presentation

Some common signs and symptoms of constipation are listed in Table 2. Development of any of these symptoms, especially in patients being treated with opioids, should be brought to the attention of the patient’s primary care provider for further evaluation.

<table>
<thead>
<tr>
<th>Constipation Signs and Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrequent bowel movements (&lt; 3/week)</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Stools that are hard, small, or dry</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Difficult/painful defecation</td>
<td>Nausea</td>
</tr>
<tr>
<td>Abdominal discomfort/bloating</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Feeling of incomplete evacuation</td>
<td>Severe, persistent refractory constipation</td>
</tr>
<tr>
<td>Bloody stools</td>
<td>New-onset or worsening constipation in elderly</td>
</tr>
</tbody>
</table>

Items in bold are considered alarm symptoms and should be reported to the physician immediately.
Treatment

Early prevention and treatment of opioid-induced constipation should focus on dietary changes and laxatives to promote regular bowel movements. If constipation persists, four agents currently on the market have been approved for the treatment of opioid-induced constipation.

**Lubiprostone (Brand name: Amitiza®)**

This medication acts locally within the gastrointestinal tract to increase fluid secretion within the intestine and promote fecal transit. Usual dosage is one 24 mcg capsule by mouth twice daily taken with food and water to decrease nausea. The capsule should be swallowed whole (do not break or chew). Monitor for signs of dyspnea and hypotension. Contraindicated in patients with a known or suspected GI obstruction.

**Methylnaltrexone (Brand name: Relistor®)**

This medication blocks opioid receptor activity in peripheral tissues to inhibit opioid-induced gastrointestinal effects without affecting the analgesic properties of opioids. Usual dosage is 450 mg by mouth once daily or 12 mg via subcutaneous injection once daily. This agent may cause symptoms of opioid withdrawal (abdominal pain, anxiety, chills, excessive sweating, etc.) It is contraindicated in patients with a known or suspected GI obstruction.

**Naldemedine (Brand name: Symproic®)**

This medication is an opioid antagonist that blocks opioid receptor activity in peripheral tissues to inhibit opioid-induced gastrointestinal effects. Usual dosage is 0.2 mg by mouth once daily. This agent should be discontinued if opioid medication therapy is stopped. Naldemedine may cause symptoms of opioid withdrawal and is contraindicated in patients with a known or suspected GI obstruction.

**Naloxegol (Brand name: Movantik®)**

This is an opioid receptor antagonist formulated to limit its ability to cross the blood-brain barrier and affect analgesia. At recommended doses, this agent exerts its effect in peripheral tissues to inhibit opioid-induced gastrointestinal effects. Usual dose is 25 mg by mouth once daily, which can be reduced to 12.5 mg by mouth once daily if patient is unable to tolerate the full dose. This agent should be discontinued if opioid medication therapy is stopped. Monitor for signs of severe abdominal pain and/or diarrhea. Naloxegol may also cause symptoms of opioid withdrawal and is contraindicated in patients with a known or suspected GI obstruction.

Summary

Constipation is a problem that is already a prevalent issue in the elderly. With older adults using opioid analgesics to treat pain for multiple issues, constipation due to these medications is of increasing concern. Recent medications advances target this particular form of constipation and may be appropriate for use in this population. If you have any questions about the use of these medications, don’t hesitate to reach out to your Neil Medical Group Pharmacist.

---

*Article by Josh Baugh, PharmD Candidate*

*Wingate University School of Pharmacy*
To all the Pharm Notes Family,

Many of you know that I have a true love for the dementia resident and am an advocate for non-pharmacologic interventions for their behaviors. I found this recently and thought it was really worthy of sharing.

Alzheimer’s Communication

5. Never say “Remember”. Instead Reminisce.
7. Never say “You Can’t”. Instead say what they Can Do.

Till next time........

Cathy Fuquay
Pharm Notes Editor