Unituxin™ (dinutuximab) is the first drug approved specifically for pediatric neuroblastoma. Dinutuximab was approved March 10, 2015 as first-line therapy in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis retinoic acid (RA). The FDA granted dinutuximab orphan drug status because of the relative rarity of the pediatric neuroblastoma.

Dinutuximab’s specific activity against neuroblastoma is an exciting and possibly life-changing treatment option for a disease that is classically treated by chemotherapy, surgery, radiotherapy, and stem cell transplant.

Dinutuximab binds to glycolipid GD2. GD2 is expressed on neuroblastoma cells as well as other cells of neuroectodermal origin. Once bound to GD2, dinutuximab induces cell lysis through antibody-dependent cell-mediated cytotoxicity as well as complement-dependent cytotoxicity.

In clinical trials, dinutuximab significantly improved event-free survival (EFS) scores after three years (29% vs 44%). Overall survival was also significantly better in the dinutuximab-treated group after seven years (73% vs 58%, respectively). Patients were randomly assigned to receive either RA alone or dinutuximab in combination with IL-2, GM-CSF, and RA. This trial included 226 pediatric patients with high risk neuroblastoma. EFS was defined as time from randomization to relapse, disease progression, other malignancy, or death. All patients in the study received prior therapy of induction chemotherapy, maximum surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and radiation therapy. This study was limited by its small number of participants making results hard to generalize to all pediatric patients with neuroblastoma.

Adverse events most commonly reported during dinutuximab therapy include infusion reactions, pain and peripheral neuropathy, capillary leak syndrome, hypotension, infection, neurological disorders of the eye, bone marrow suppression, electrolyte abnormalities, immunogenicity, and atypical hemolytic uremic syndrome.

Dosage recommendations for dinutuximab are 17.5 mg/m²/day administered as an IV infusion over 10-20 hours for 4 consecutive days for a maximum of 5 cycles. Because of the pain reactions, pretreatment pain management before the infusion of dinutuximab is required (see table below).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal saline</td>
<td>10 mL/kg IV</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>50 mg/kg IV</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>0.5 mg/kg IV</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>10-15 mg/kg (max 650 mg)</td>
</tr>
</tbody>
</table>

By Hugh Daniels, PharmD Candidate

References:
PATIENT INFORMATION:
Constipation—An Overview

What is constipation?
- Less than 3 bowel movements a week.
- More than 3 days have passed since your last bowel movement.
- Difficulty passing stools, such as:
  - Straining to have a bowel movement
  - Passing hard or small stools
  - Incomplete bowel emptying

What causes constipation?
- Certain medications and conditions
- Dehydration
- Pregnancy
- Menopause
- A diet low in fiber, carbs or calories

When should I seek medical attention?
Consult your healthcare provider if:
- Constipation has lasted for several weeks
- Constipation lasts longer than 7 days despite the use of laxatives
- Rectal bleeding occurs while using laxatives
- Constipation occurs in a child younger than 2 years of age

What can I do to treat constipation?
Initial Management:
- Increase dietary fiber
  - Foods that are high in fiber include fruits, vegetables, and whole grains
    - 1 cup raw spinach = 3.5 g fiber
    - ½ cup brown rice = 5.5 g fiber
  - 1 cup whole wheat spaghetti = 5.6 g fiber
  - 1 medium banana = 3 g fiber
  - 1 large apple = 4.5 g fiber
- Avoid foods with little fiber such as cheese, meat, and processed foods
- Increase fluid intake
  - Drink about 2 liters (68 ounces) of water per day
- Increase exercise

Medications:
Laxatives may be used in addition to lifestyle modifications, for immediate relief of constipation

What laxative should I try first?
Laxative options should be tried in descending order; 2nd and 3rd line options may be tried if the previous laxative option fails to alleviate symptoms. (See table below for treatment recommendations.)

Metamucil® (psyllium) and Citrucel® (methylcellulose):
- Should be taken with a full glass of water
- Should be avoided if you have difficulty swallowing or are on a fluid restricted diet
- Should not be used to treat constipation caused by opioids

Senokot® (sennosides):
- May turn urine pink, red, violet, or brown color

Enteric-coated Dulcolax® (bisacodyl):
- Do not take within 1 hour of milk, antacids or acid suppressing medications

By Alyssa Nystrom, PharmD Candidate

References:

Treatment options for Constipation

<table>
<thead>
<tr>
<th>Population</th>
<th>1st Line Treatment</th>
<th>2nd Line Treatment</th>
<th>3rd Line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children less than 2 years</td>
<td>Consult with their Primary Care Provider (PCP)</td>
<td>Consult PCP</td>
<td>Senokot® (sennosides) or oral/rectal Dulcolax® (bisacodyl)</td>
</tr>
<tr>
<td>Children age 2-6 years</td>
<td>Colace® (docusate)</td>
<td>Rectal glycerin suppository</td>
<td>Senokot® (sennosides) or oral/rectal Dulcolax® (bisacodyl)</td>
</tr>
<tr>
<td>Children age 6-12 years</td>
<td>Citrucel® (methylcellulose), Metamucil® (psyllium) or Colace® (docusate)</td>
<td>Rectal glycerin suppository or MiraLax® (polyethylene glycol 3350)</td>
<td>Senokot® (sennosides) or oral/rectal Dulcolax® (bisacodyl)</td>
</tr>
<tr>
<td>Adults</td>
<td>Citrucel® (methylcellulose), Metamucil® (psyllium) or Colace® (docusate)</td>
<td>Citrucel® (methylcellulose), Metamucil® (psyllium) or Colace® (docusate)</td>
<td>Senokot® (sennosides) or oral/rectal Dulcolax® (bisacodyl)</td>
</tr>
<tr>
<td>Pregnant Women</td>
<td>Dietary Changes</td>
<td>MiraLax® (polyethylene glycol 3350)</td>
<td>Senokot® (sennosides) or oral/rectal Dulcolax® (bisacodyl)</td>
</tr>
<tr>
<td>Lactating Women</td>
<td>Colace® (docusate)</td>
<td>MiraLax® (polyethylene glycol 3350)</td>
<td>Senokot® (sennosides) or oral/rectal Dulcolax® (bisacodyl)</td>
</tr>
<tr>
<td>Constipation due to opioid use</td>
<td>Colace® (docusate) plus Senokot® (sennosides) or oral/rectal Dulcolax® (bisacodyl)</td>
<td>Consult PCP</td>
<td>Consult PCP</td>
</tr>
</tbody>
</table>

Volume 19, Issue 5
What is dofetilide?
Dofetilide is a prescription medication that helps to treat irregular heartbeats such as atrial fibrillation and atrial flutter. Taking dofetilide will help keep your heart beating normally.

Dofetilide is for people with many symptoms caused by their irregular heartbeat. Your healthcare provider might also use it to make your irregular heartbeat normal again.

What do I need to tell my doctor before I start dofetilide?
Dofetilide can interact with many different medications. You will need to give your healthcare provider a complete list of all of your medications, herbal supplements, vitamins, and over-the-counter products such as Tylenol® (acetaminophen) or Advil® (ibuprofen) before starting. This will ensure that you do not take any drugs that will interact with dofetilide.

Dofetilide can worsen irregular heartbeats in some people. You will need to tell your healthcare provider if you have a long QT interval before starting dofetilide.

Medications you should not take while on dofetilide due to an increased risk of side effects:
- Cimetidine
- Verapamil
- Ketoconazole
- Trimethoprim
- Prochlorperazine
- Megestrol
- Dolutegravir
- Hydrochlorothiazide alone or in combination with other medications

Why do I have to stay in the hospital when I start dofetilide?
When you start dofetilide, there is a risk of causing a type of irregular heartbeat called torsades de pointes, which can lead to death. The risk of having torsades de pointes is increased if your kidneys do not work very well. To make sure that you do not get torsades de pointes, you will need to stay at the hospital for heart monitoring. Your healthcare provider will also do a blood test to check your kidney function to make sure that your kidneys are working well.

You will need to be in the hospital for three days to check your heart and kidneys. If your kidneys and heart are doing well, then you can go home.

How will I know if dofetilide is right for me?
You should talk to your healthcare provider before you start taking dofetilide to make sure it is right for you. There are some reasons your healthcare provider might not want you to take dofetilide, such as kidney problems or if you take medications that interact with dofetilide.

If you have any reactions such as hives or have trouble breathing after taking dofetilide, you might be allergic to it. If you think you might have an allergy to dofetilide, you should go to your local emergency room.

What are some side effects of dofetilide?
The most common side effects of dofetilide are headache, chest pain, and dizziness. However, very few people have these side effects when taking dofetilide.

Some side effects may indicate a serious problem. If you have extreme chest pain, dizziness, or headaches, you should go to your local emergency room.

What are some serious side effects of dofetilide?
In rare cases, dofetilide can lead to serious side effects such as seizures or death. You can lower your risk of serious side effects by drinking plenty of fluids and taking your medication as instructed.

If you experience extreme dizziness, a racing heart, or prolonged vomiting or diarrhea, report to the nearest emergency department immediately. These may be signs of serious side effects.

How should I take dofetilide?
It is important that you take dofetilide at the same time every day. You may take dofetilide with or without food.
Levomilnacipran is a newer medication on the market to treat major depressive disorder (MDD). It is a potent, selective serotonin and norepinephrine reuptake inhibitor (SNRI). Levomilnacipran differs from other SNRI medications in that it has two-fold greater potency for norepinephrine reuptake inhibition than for serotonin reuptake inhibition. Other medications within the same class are ten times less selective for norepinephrine than levomilnacipran. There is debate whether SNRIs are superior to SSRIs, and levomilnacipran may have superior efficacy due to its greater effect on the norepinephrine system. Clinical trials showed levomilnacipran to function like older tricyclic antidepressants, but without the safety and tolerability issues. Levomilnacipran is the active enantiomer of milnacipran, a drug used to treat fibromyalgia in adults. Unlike milnacipran, levomilnacipran is an extended-release formulation and thus is taken once daily. It was approved for use in the treatment of MDD by the FDA on July 26, 2013.

Levomilnacipran was effective in reducing depression at two dosages in a phase III, randomized, double-blind, fixed-dose, placebo-controlled study. The study used the Montgomery-Asberg Depression Rating Scale (MADRS) to evaluate the level of depression of the participants. This ten-week study (1-week placebo run-in period, 8-week double-blind treatment, 1-week down-taper) included adult patients suffering from MDD. The intent-to-treat analysis included 185 participants in the placebo, 185 participants in the 40 mg levomil-nacipran group, and 187 participants in the 80 levomilnacipran mg group.

Levomilnacipran patients had clinically significant improvements in MADRS scores at 40 mg and 80 mg doses versus placebo. The difference was apparent after as few as four weeks into the treatment phase. Using the Sheehan Disability Scale (SDS), which measures level of functional disability, a significant decrease in disability was observed in the treatment groups compared to placebo. However, only the 80 mg dose group showed a statistically significant difference occurring at week 6. The main limitations of this study were the small sample size, the short treatment duration, and the lack of a 120 mg dose group. This study did, however, demonstrate a significant improvement of depression in those participants receiving levomilnacipran.

In another study, levomilnacipran was effective in reducing depression at all therapeutic dosage strengths. In an 11-week study with 8 weeks of double-blind treatment, participants were randomly assigned to placebo (n=179), 40 mg levomilnacipran (n=181), 80 mg (n=181), or 120 mg (n=183). Each levomilnacipran group showed improvement relative to placebo, and after sensitivity analyses, each dose strength produced a statistically significant improvement in depression symptoms. An observed advantage over placebo was seen within 4 weeks in both the 80 mg and the 120 mg dosing groups. Improvements in the SDS score were significantly greater for the 80 mg and 120 mg dose groups also. This study had similar results to the one above, but the additional dosage group was also effective over placebo. The main limitations in this study were small sample size and short duration of the study.

Levomilnacipran causes the common GI side effects seen with most SNRIs like nausea, vomiting, and constipation. The main adverse effects that differ with levomilnacipran are cardiovascular and sexual effect. Levomilnacipran produces tachycardia, palpitations and increased heart rates in 5%-6% of patients. It also can cause erectile dysfunction and ejaculation disorder in male patients with a higher incidence than other SNRIs. This effect is commonly dose-related with higher doses causing sexual effects more frequently. Another unique side effect is hyperhidrosis, which occurs in about 9% of patients.

MAOIs should not be taken while on levomilnacipran and a brief drug-free period should take place before or after use of MAOIs. Because of the increased risk of serotonin syndrome, linezolid and methylene blue should not to taken while on levomilnacipran. Along with the other SSRIs and SNRIs, levomilnacipran carries a black box warning about increased suicidal ideations and behaviors in children, adolescents and young adults.

The recommended dose for levomilnacipran is 40 mg to 120 mg once daily. It can be taken with or without food, and the capsules should be swallowed whole. A patient should be started on 20 mg daily for two days before increasing to 40 mg daily. Depending on efficacy and tolerability, patients may continue to increase by 40 mg every two days until they reach their goal dosage or the maximum dose of 120 mg daily. Patients with moderate renal impairment should not exceed 80 mg levomilnacipran, and patients with severe renal impairment should not exceed 40 mg levomilnacipran.

By Amy Eliason, PharmD Candidate

References on Page 5
Fetzima® References (from page 4)


Cresemba® References (from page 7)


Ulcerative Colitis References (from page 6)


http://quotesideas.com/wp-content/uploads/2015/05/280528512ap0ahmep.gif
Ulcerative colitis (UC) is an inflammatory condition of the large intestine, which is also called the colon. The surface of the colon becomes very inflamed, and open sores (ulcers) develop. Often, mucus and pus leak from the ulcers and causes abdominal discomfort and diarrhea.

**Causes of UC**
The exact causes of UC are unknown; however, scientists believe that UC is due to a combination of factors.
- **Overactive Immune System:** The human digestive system is protected by our immune system to fight bacteria and viruses. In patients with UC, the immune system can be “triggered” by a bacteria or virus and then become hypersensitive to food and other non-harmful particles long after the infection is controlled. This causes irritation in the colon.
- **Genetics:** There is no direct genetic link for patients with UC; however, UC commonly runs in families. The exact reason is unknown.
- **Environment:** There is some debate that environmental factors, such as certain medications and high-fat foods, may put a person at a higher risk for developing UC. However, the risk appears to be very small.

**Risk Factors**
- Age between 15-30 years, or older than 60 years
- Having a family member with UC or other inflammatory bowel disease
- Having Jewish ancestors

**Signs & Symptoms**
- Diarrhea containing blood or pus
- Abdominal pain (mild to severe cramping)
- Frequently having the sudden urge to have a bowel movement
- Feeling exhausted or tired
- Loss of appetite
- Weight loss
- Anemia (a condition of having less red blood cells)
- Rash (less common)
- Joint pain (less common)

**Diagnosis of UC**
Doctors typically obtain a full medical history and perform a physical exam variety of tests to make a diagnosis of UC.
- **Blood test:** This tests for signs of infection and monitors for anemia, which can occur if there is bleeding in the colon.
- **Fecal matter test:** This test looks for signs of bacteria and viruses and is done to make sure that an infection is not the cause of a person’s symptoms.
- **Sigmoidoscopy or colonoscopy:** This test allows the doctor to get a visual picture of the colon. A sigmoidoscopy consists of a small tube with a light and camera being inserted into the anus and evaluating the rectum and lower colon. A colonoscopy is very similar, but looks at the whole colon.
- **Biopsy:** During a sigmoidoscopy or colonoscopy, a small sample of tissue may be taken from the colon to evaluate for signs of disease.

**Treatment Goals**
- Reduce severity and frequency of symptoms
- Achieve and maintain remission, a period of time without symptoms of ulcerative colitis

**Treatment Options**

**Medications**
- Aminosalicylates (5-ASA)
  - Reduce inflammation in the colon and help maintain remission
  - Examples include oral and rectal sulfasalazine and mesalamine.
- Corticosteroids
  - Reduce inflammation, control the immune system, and help achieve remission in more severe ulcerative colitis cases
  - Examples include oral and rectal methylprednisolone and prednisone and rectal budesonide
- **Immunomodulators**
  - Decrease immune system activity, which helps prevent inflammation and maintain remission
  - Examples include oral azathioprine and 6-mercaptopurine
- **Biologics**
  - Reduce inflammation and help achieve remission in people who have not responded well to other medications
  - Examples include IV Remicade® (infliximab) and Entyvio® (vedolizumab) and injection Humira® (adalimumab) and Simponi® (golimumab)
- **Surgery**
  - Some people unable to control UC with medications may need to have surgery to remove a portion or the entire colon and rectum.
  - The small intestine may be connected to an opening in the abdomen and waste is deposited into an external bag outside the body.
  - A different procedure removes the colon and creates a small pouch from the small intestine and connects it to the anus. There is no need for an external bag with this surgery.

**Changes in Eating Habits**
Although food does not cause ulcerative colitis, avoiding certain foods can help prevent symptom flares. Foods that can contribute to symptom flares:
- High-fiber foods: nuts, vegetable skins, popcorn, etc.
- Spicy foods
- Carbonated drinks

By Jennifer McVeigh, PharmD Candidate

References on Page 5
Cresemba® (isavuconazonium sulfate) is an azole antifungal approved for the treatment of invasive aspergillosis and mucormycosis in patients 18 years of age or older. Aspergillosis is an opportunistic fungal infection and typically affects the respiratory system, whereas mucormycosis is a rare soil-based fungal infection. The FDA designated isavuconazonium sulfate as an orphan drug due to limited treatment options for invasive aspergillosis and mucormycosis.

Isavuconazonium sulfate is the prodrug of isavuconazole. Isavuconazole inhibits the synthesis of ergosterol through inhibition of lanosterol 14-alpha-demethylase, an enzyme that converts lanosterol to ergosterol. Decreased production of ergosterol weakens the integrity of the fungal cell wall.

The efficacy and safety of isavuconazonium sulfate was demonstrated in two phase III clinical trials. Isavuconazonium sulfate was an effective treatment for invasive mucormycosis and was non-inferior to voriconazole for the treatment of invasive aspergillosis.

**Trial 1:**
All-cause mortality and end-of-treatment success was assessed for patients with suspected or proven invasive aspergillosis. The trial included 231 individuals receiving isavuconazonium sulfate (N=123) or voriconazole (N=108). The average duration of treatment for either group was 47 days with a maximum treatment duration of 84 days. All-cause mortality through day 42 was 18.7% in patients receiving isavuconazonium sulfate and 22.2% for patients treated with voriconazole (adjusted treatment difference -2.7; 95% CI: -13.6 to 8.2). End-of-treatment success was observed in 35% of patients receiving isavuconazonium sulfate and in 38.9% of those treated with voriconazole (adjusted treatment difference -4.0; 95% CI: -16.3 to 8.4). The study was limited by the small number of patients, of which the majority were Caucasian (78%) and male (60%).

**Trial 2:**
All-cause mortality through day 42 and end-of-treatment success was similar among individuals receiving isavuconazonium sulfate as their primary treatment and those who had been refractory or intolerant to previous antifungal therapy. All-cause mortality was 33-46% and end-of-treatment success was 20-36%. Therefore, isavuconazonium sulfate was determined to be an effective primary treatment option for invasive mucormycosis and for patients refractory or intolerant to previous antifungal therapies. The study was limited by its open-label design and also the small number of patients (37). The majority of the patients were Caucasian (68%), male (81%), and had fungal disease involving the lungs (59%), which limits the generalizability of the results.

The most common adverse reactions reported during clinical trials included nausea (26%), vomiting (25%), diarrhea (22%), headache (17%), elevated liver chemistry tests (16%), hypokalemia (14%), constipation (13%), dyspnea (12%), peripheral edema (11%), and back pain (10%). Isavuconazonium sulfate is a substrate and moderate inhibitor of CYP3A4. Serum levels of isavuconazonium sulfate can be significantly altered when administered with other strong CYP3A4 inhibitors or inducers and therefore is contraindicated in persons receiving such medications. Isavuconazonium sulfate is also contraindicated in persons with known hypersensitivity to isavuconazonium sulfate or who have a history of familial short QT syndrome. Warnings associated with isavuconazonium sulfate include hepatic enzyme elevation, infusion related reactions, hypersensitivity reactions and fetal toxicity.

**By Alyssa Nystrom, PharmD Candidate**

**Dosage Forms and Strengths:**
- 186 mg isavuconazonium sulfate capsule (equivalent to 100 mg isavuconazole)
- 372 mg isavuconazonium sulfate single-dose vial for injection (equivalent to 200 mg isavuconazole)
- Intravenous and oral formulations are bioequivalent

**Dosage and Administration:**
- Loading dose:
  - 372 mg isavuconazonium sulfate orally or intravenously every 8 hours for 6 doses

Maintenance dose:
- 372 mg isavuconazonium sulfate orally or intravenously once daily starting 12 to 24 hours after the last loading dose
- Oral capsules can be taken with or without food

**Special Populations**

**Pregnancy and Lactation**
- Category C. Fetal development abnormalities were seen in animal studies and in clinical trials of other azole antifungals.
- Excreted in milk of lactating rats. Avoid breastfeeding while taking isavuconazonium sulfate.

**Renal Impairment**
- No renal dose adjustments needed

**Hepatic Impairment**
- No hepatic dose adjustments for mild to moderate impairment (Child-Pugh Class A and B)
- Safety and efficacy not established in patients with severe hepatic impairment (Child-Pugh Class C). Weigh risks versus benefits before use.

References on Page 5
PATIENT INFORMATION:
Choline: A Memory Boosting Miracle?

Over the years, there have been claims about different foods and supplements improving health. We see them published all over the media. Low levels of a nutrient called choline have been associated with poor memory function. As a result, one such claim is that increased choline intake may boost memory function.

What is choline?
Choline is an essential nutrient related to B vitamins that is found naturally in human bodies.

What does choline do?
Choline is made into acetylcholine, a chemical compound that is necessary for proper nerve function. The fetal brain requires choline for proper development. It is also used to make certain molecules, which are needed to prevent buildup of cholesterol in the liver.

Where is choline found?
There are many dietary sources of choline. It is also available as an over-the-counter supplement.

How much choline do I need?
In general, people get adequate amounts of choline from their diet and do not need to take supplements. The recommended daily amount of choline is between 425 mg and 550 mg. Choline supplements are generally regarded as safe. However, doses over 3.5 grams per day for adults may be unsafe and increase the risk that adverse effects may occur.

What are the side effects of choline?
Adverse effects that people may experience after consuming too much choline include low blood pressure, fatty stools, nausea, vomiting, diarrhea or constipation, and dizziness & vertigo. Adverse effects usually vary person-to-person. People with certain conditions like Parkinson’s disease, liver, or kidney disease should avoid taking choline supplements, but dietary choline is okay. In special populations, like children or pregnant women, choline is considered to be likely safe for use.

Is choline used for anything else?
Choline has been used for many other things, including liver disease, high cholesterol, depression, body building, and prevention of neural tube defects.

Will it interact with any other foods or medications?
There may be a minor interaction between choline and a medication called atropine, consult your doctor before starting choline. There are no other known interactions between choline and foods or other supplements.

Does using choline actually work?
Choline has been studied in clinical trials in people with dementia and Alzheimer’s disease. Choline has not been shown to work to improve memory function or to prevent memory loss. It is possibly effective to relieve asthma symptoms for some people. It also might be useful to decrease the risk of neural tube defects. Everything else that choline might be used for has not been proven to be effective.

By Casey Lauver, PharmD Candidate


http://www.life-enhancement.com/magazine/article/2378-choline-detoxifies-and-proTECTS