PATIENT INFORMATION:
Off the Clock: Non-24-Hour Sleep-Wake Disorder

Non-24-hour sleep-wake disorder (non-24) is most common among the completely blind people. Because the blind cannot perceive light, their bodies have a difficult time knowing when it is nighttime. This lack of perception skews the normal 24-hour long sleep-wake cycle into a slightly longer cycle. Eventually, the body starts to crave sleep during the day and to stay alert at night.

Getting enough quality sleep is very important for overall health. Studies have shown that people who suffer from circadian rhythm disorders and get less than six hours of sleep each night are more likely to have:

♦ Heart disease (15% higher risk)
♦ Strokes (almost 2x higher risk)
♦ Hypertension (50% higher risk)

Hetlioz™ (tasimelteon) was approved in 2014 and is the first drug that treats non-24. Tasimelteon stimulates melatonin receptors in the brain. These receptors regulate sleep cycles related to light perception. A 20 mg daily dose of tasimelteon at bedtime helps correct sleep cycles in some people by helping them fall asleep quicker and stay asleep longer. The most common side effects of tasimelteon include strange dreams and headache.

Some studies suggest that combination therapy with light and melatonin may help manage non-24. Morning exposure to bright light may decrease the amount of melatonin produced during the day. When morning light therapy is used with nighttime melatonin, some people’s circadian rhythms may self-regulate.

Melatonin used alone may help non-24 sufferers sleep longer. However, this does not prevent daytime melatonin production, so daytime fatigue is not decreased when melatonin is used by itself.

While caffeine may help those with non-24 feel less tired during the day, it does not help retrain the body’s circadian rhythm. So caffeine does not alter a person’s sleep cycle and does not treat non-24-hour sleep-wake disorder.

By Micah Nevin, PharmD Candidate

REFERENCES:

Hypercholesterolemia is most frequently treated with statin therapy. In some patients, statin therapy is insufficient to control cholesterol levels as monotherapy or it may not be tolerated due to serious adverse effects, such as myalgia or rhabdomyolysis. PCSK9 inhibitors are a new drug class designed for patients who require additional medication for better control of their cholesterol levels as well as for patients who cannot tolerate statin drugs.

The PCSK9 (protein convertase subtilisin/kexin type 9) gene controls the production of secretory proteins and receptors including those for cholesterol. Highest concentrations of PCSK9 are found in the liver, kidneys, and atherosclerotic plaques. PCSK9 influences cholesterol levels by regulating the number of LDL receptors found on the cellular membrane.

PCSK9 inhibitors are human monoclonal antibodies designed to inhibit overactive PCSK9, leading to fewer LDL receptors and lowering demand for LDL cholesterol. A decrease in demand for LDL will reduce the amount of LDL produced in the body.

Evidence suggests that statins up-regulate PCSK9 activity, limiting the benefits of statin therapy. PCSK9 inhibitors block this negative effect of statins and improve lipid control.

PCSK9 inhibitors significantly improve patient outcomes when used as monotherapy or as an adjunct to statin therapy. Two trials compared the LDL-lowering effects of PCSK9 inhibitors to ezetimibe and found ≥50% reduction in LDL levels in both PCSK9 treatment groups. The ODESSEY-monotherapy trial evaluated alirocumab taken 75 mg every 2 weeks, and the MENDEL-2 trial studied evolocumab 140 mg every 2 weeks or 420 mg every month.

The ODESSEY-long term and the OSLER-1 and 2 trials demonstrated ≥60% improvement in LDL levels in the PCSK9 treatment groups compared to baseline. PCSK9 inhibitors were given as adjuncts to standard therapy for hypercholesterolemia. The ODESSEY-long term trial reported an average LDL level of 48 mg/dL by week 24 in the PCSK9 treatment arm. Additional trial efficacy data is available in Table 1 (page 3).

The majority of adverse effects from PCSK9 inhibitors are considered mild to moderate in severity. Few subjects withdrew from the trials due to intolerable side effects. Nasopharyngitis is the most common side effect of PCSK9 inhibitors and other monoclonal antibodies. The incidence of adverse effects with PCSK9 inhibitors.

PCSK9 inhibitors significantly lower lipid levels and have a lower risk of myalgia than statin therapy. The risk for cardiovascular events was reduced slightly in patients taking PCSK9 inhibitors in clinical trials. However, more studies are needed to determine the long-term benefits of these drugs.

By Briana Cosca, PharmD Candidate

REFERENCES:


Tables on Page 3
### TABLE 1: Additional Efficacy Data: PCSK9 Inhibitor results compared to baseline lab values

<table>
<thead>
<tr>
<th>Name of Trial</th>
<th>ODESSEY-monotherapy</th>
<th>ODESSEY-long term</th>
<th>OSLER trials&lt;sup&gt;4,5&lt;/sup&gt;</th>
<th>MENDEL-2&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>Alirocumab vs. ezetimibe</td>
<td>Alirocumab + ST vs. ST alone</td>
<td>Evolocumab vs. ezetimibe</td>
<td>Evolocumab + ST vs. ST alone</td>
</tr>
<tr>
<td>Duration of treatment for efficacy</td>
<td>24 weeks</td>
<td>24 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>103</td>
<td>2341</td>
<td>4465</td>
<td>614</td>
</tr>
<tr>
<td>Dose of PCSK9 inhibitor</td>
<td>75 mg every 2 weeks</td>
<td>150 mg every 2 weeks</td>
<td>140 mg every 2 weeks or 420 mg every month</td>
<td>140 mg every 2 weeks</td>
</tr>
<tr>
<td>Non-HDL</td>
<td>↓ 40.6%</td>
<td>↓ 51.6%</td>
<td>↓ 52%</td>
<td>↓ 50.2%</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>↓ 36.7%</td>
<td>↓ 52.8%</td>
<td>↓ 47.3%</td>
<td>↓ 47%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>↓ 11.9%</td>
<td>↓ 15.6%</td>
<td>↓ 12%</td>
<td>↓ 9.2%</td>
</tr>
<tr>
<td>Lipoprotein a</td>
<td>↓ 16.7%</td>
<td>↓ 29.3%</td>
<td>↓ 25.5%</td>
<td>↓ 18.4%</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>↓ 29.6%</td>
<td>↓ 37.8%</td>
<td>↓ 36.1%</td>
<td>n/a</td>
</tr>
<tr>
<td>HDL</td>
<td>↑ 6%</td>
<td>↑ 4%</td>
<td>↑ 7%</td>
<td>↑ 3.9%</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>↑ 4.7%</td>
<td>↑ 4%</td>
<td>↑ 4.2%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*ST = Standard Therapy*

### TABLE 2: Adverse Effect Incidence with PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Name of Trial</th>
<th>ODESSEY-monotherapy&lt;sup&gt;3&lt;/sup&gt;</th>
<th>ODESSEY-long term&lt;sup&gt;6&lt;/sup&gt;</th>
<th>OSLER trials&lt;sup&gt;4,5&lt;/sup&gt;</th>
<th>MENDEL-2&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Alirocumab</td>
<td>Alirocumab</td>
<td>Evolocumab</td>
<td>Evolocumab</td>
</tr>
<tr>
<td>Dose</td>
<td>75 mg every 2 weeks</td>
<td>150 mg every 2 weeks</td>
<td>140 mg every 2 weeks or 420 mg every month</td>
<td>140 mg every 2 weeks</td>
</tr>
<tr>
<td>No. of patients</td>
<td>52</td>
<td>1550</td>
<td>2976</td>
<td>153</td>
</tr>
<tr>
<td>Any side effect</td>
<td>69%</td>
<td>81%</td>
<td>69.2%</td>
<td>48%</td>
</tr>
<tr>
<td>Serious side effects</td>
<td>&lt;1% (2 patients)</td>
<td>18.7%</td>
<td>7.5%</td>
<td>2%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12%</td>
<td>13%</td>
<td>9.4%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>5.8%</td>
<td>2.7%</td>
<td>3%</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
<td>6%</td>
<td>5.7%</td>
<td>3.6%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1%</td>
<td>5.9%</td>
<td>4.3%</td>
<td>7%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2%</td>
<td>5.4%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2%</td>
<td>7.4%</td>
<td>5.4%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
HIV (Human Immunodeficiency Virus) targets the immune system, reducing the body’s ability to fight infections and diseases. Many people with HIV do not know they have the disease until they are tested.

HIV can lead to AIDS (Acquired Immune Deficiency Syndrome). Not everyone who has HIV will get AIDS. HIV and AIDS are chronic diseases, meaning they last a lifetime.

People with AIDS have low CD4 T-cells. These cells are a type of white blood cell that fights infection in the body. Since AIDS is the final stage of HIV, the immune system is at its weakest in a person with AIDS. A person with AIDS is more likely to get certain infections, called opportunistic infections.

**HOW DOES SOMEONE GET HIV/AIDS?**
- HIV/AIDS is spread by contact with body fluids (such as blood, semen) that may contain the virus.
- Cuts or sores on the body or in the mouth is one way the virus enters the body.

**WHO IS MOST AT RISK?**
- Men who have intercourse with other men
- Anyone who has unprotected intercourse of any type
- People who share or use unclean needles

**PREVENTION METHODS**
- Barrier contraceptives (condoms)
- Avoid using unclean needles
- Avoid needle sharing
- Avoid using other people’s hygiene products such as toothbrushes

**SIGNS & SYMPTOMS**
HIV/AIDS can be undetected for months or even years. Signs and symptoms are not always specific but can include:
- Fatigue
- Rash
- Headache
- Nausea
- Upset stomach and diarrhea
- Night sweats

**HIV & AIDS MANAGEMENT**
Patients with HIV work with their healthcare providers to come up with the best treatment plan. Anti-retroviral therapy uses drugs that decrease the viral load, or amount of the HIV virus in the body.

Throughout the course of treatment, the doctor will check viral load and CD4 counts. HIV/AIDS status is assessed with these two values. Viral load and CD4 counts are also used to check how well HIV/AIDS medications are working.

There is no “normal range” for the viral load. The goal is to have undetectable levels, under 45-70 copies of the virus in 1 mL of blood. The desirable CD4 count range is between 600 and 1500 CD4 cells per mL of blood. A person with a CD4 count of 200 cells/mL or less may have progressed to AIDS.

**TREATMENT OPTIONS**
Patients with HIV need to take their medications exactly as directed, otherwise the virus can become resistant to the medications. Drugs are no longer effective against HIV/AIDS when resistance develops. This makes HIV harder to treat. Even one or two missed doses of HIV medications can result in resistance.

HIV/AIDS treatment typically includes more than one medication. Drugs from different classes are used to attack the virus in different ways.

Some medications may have to be taken more than once a day. Some of the medicines need to be taken with food, while others should be taken on an empty stomach. Side effects can also differ among the medications. Patients should talk to their healthcare provider or pharmacist about their medications to ensure that they are taking their medications correctly.

**OTHER CONSIDERATIONS**
Due to a greater risk for opportunistic infections, many people may have to take additional drugs with their HIV medications, including antibiotics. Other drugs may be prescribed to manage the side effects of the HIV medications.

Non-drug ways for people with HIV/AIDS to stay healthy:
- Schedule regular checkups
- Eat a balanced diet
- Exercise
- Get plenty of rest
- Avoiding alcohol, tobacco, and illegal drugs

*By Ka Zoua Moua, PharmD Candidate*

**REFERENCES:**
3. CD4 count (or t-cell count) (10/24/2014). US Department of Veteran

*Continued on Page 5*
HIV/AIDS (from page 4)


Bexsero® (from page 6)

2015.


What is borderline personality disorder?

Borderline personality disorder (BPD) is a mental disorder characterized by unstable self-image, mood, and relationships. Some patients with BPD may harm themselves and/or have thoughts of suicide.

People with BPD often have difficulty functioning in daily life. Feelings of emptiness, poor self-image, and lack of goals make it hard for people with BPD to participate in normal activities. Some people may have trouble maintaining close relationships due to fear of losing that person or being hurt by them.

BPD can make it difficult for people to control their emotions and desires. They may have frequent, intense feelings of anger, anxiety, depression and insecurity that last up to an entire day. Lack of impulse control with BPD can lead to the person participating in risky behaviors such as unsafe sex or reckless driving.

The level of functioning and ability to control emotions in people with BPD does not change over time. BPD symptoms are not due to a person’s maturity level or cultural/social differences. BPD symptoms are not caused by drug abuse or medical conditions like a severe concussion.

Patients with BPD may also have anxiety disorders, drug or alcohol abuse disorder, or depression. People with both BPD and depression may find that antidepressant medications are less helpful in treating their depression.

How is BPD treated?

Counseling is the first option for treating most people with BPD. Therapists use techniques developed specifically for BPD and encourage their patients to take active control of their disease. BPD treatment is focused on managing each patient’s specific symptoms. Some patients receive one-on-one therapy, while others attend small group sessions.

Medications may be used to manage the more severe symptoms of BPD. Commonly used drugs include antipsychotics, such as Abilify® (aripiprazole) and Zyprexa® (olanzapine), and mood stabilizers, such as Lamictal® (lamotrigine) and Depakote® (devalproex). Medications are typically only used when a patient’s symptoms become difficult to control and are often used for only brief periods of time.

Who is at risk for BPD?

BPD is often diagnosed in teenagers or young adults. Women are more likely to be diagnosed with BPD than men—75% of BPD patients are women.

People who have a close family member (such as a parent) with BPD are more likely to have the disorder themselves. Those who experienced traumatic events as a child, such as the death of a parent or physical abuse, are also at a higher risk for developing BPD.

Common BPD myths:

I will be stuck with BPD symptoms for life.

Patients who participate in therapy and have stable, secure home lives can gain control of their symptoms. Many people with BPD live relatively normal lives.

People who harm themselves just do it for attention.

Patients with BPD may harm themselves for many reasons. Patients may believe that they are punishing themselves for being “bad” or feel like they have control over their emotional pain when they harm themselves. Some patients harm themselves by cutting or burning because they feel “numb” or “dead”. It is important to take this behavior seriously and encourage the person to seek medical attention in order to prevent permanent harm or even death.

I am just depressed or bipolar.

BPD is occasionally mistaken for bipolar disorder or depression. The most important difference between bipolar disorder and BPD is the fear of rejection felt by patients with BPD. Depression differs from BPD mainly because people with BPD experience more severe feelings of shame and negative self-image than people with depression. Mistaking BPD for either of these disorders may lead to a delay in treatment and unnecessary use of medications.

By Briana Cosca, PharmD Candidate

REFERENCES:


Until now, healthcare providers have had limited options for preventing and controlling outbreaks of Meningococcal Group B infections. Bexsero® is a safe and effective vaccine for this use.

Bexsero® (4CMenB) is a recombinant vaccine for the prevention of meningococcal disease caused by Neisseria meningitidis serogroup B. Currently, Bexsero® is only approved for individuals who are at an increased risk of being infected with serogroup B meningococcal disease. Individuals exposed to a serogroup B meningococcal disease outbreak (usually on college campuses) have an increased risk for infection and should receive Bexsero®. The Advisory Committee on Immunization Practices is currently considering broadening Bexsero® use in adolescents and young adults. Bexsero® is approved for use in individuals age 10-25 years old. This age range is relatively conservative considering Bexsero® was approved in Europe for infants starting at 2 months of age.

There are multiple vaccination options available for meningococcal serogroups A, C, W, and Y; however, until now there has only been one serogroup B vaccine available in the United States, Trumenba®. Bexsero® has advantages over Trumenba®. Bexsero® is a two-shot series with a flexible dosing schedule (injections are given at least one month apart), whereas Trumenba® is a three-shot series administered at 0, 2, and 6 months.

The most common meningococcal serogroups in the United States are B, C, and Y. The Centers for Disease Control and Prevention (CDC) reported that, through 2002-2011, there were 402 cases of serogroup B, 305 cases of serogroup C, 365 cases of serogroup Y, and 76 cases of the other serogroups. Bexsero® fills an important niche for controlling meningococcal serogroups.

Bexsero® produced immunogenicity after two to three doses in a multicenter, randomized, placebo-controlled trial. The study included 1631 patients age 11-17 years old with no history of meningococcal disease or serogroup B vaccination. Patients received either three placebo injections or one, two, or three doses of Bexsero®. Injections were given in one month intervals, except for one study group who received two doses of Bexsero® two months apart. When participants were not scheduled to receive a Bexsero® dose, they were administered a placebo to maintain blinding.

Titers were measured for three different surface proteins, factor H binding protein, neisserial adhesin A, and NZ outer membrane vesicle components. After one dose of Bexsero®, at least 93% of participants had protective antibody levels for all three titers. A second dose produced >99% protective antibody levels for all three titers regardless of the time between the two doses. The third dose did not increase the proportion of participants achieving protective titers. Based on these results, the authors concluded that two doses of Bexsero® given to healthy adolescents could impart substantial protection against meningococcal serogroup B disease. This study was conducted in Chile, so the results must be used cautiously since nearly all participants were Hispanic and the study results may not be reproducible in other populations.

Local adverse effects of Bexsero® include pain, erythema, induration, and swelling. Systemic side effects include fatigue, malaise, nausea, myalgia/arthralgia, headache, and fever.

Meningococcal disease is life threatening, but Bexsero® is a viable option to immunize and protect individuals at risk for serogroup B meningococcal infections. Bexsero® may soon become more broadly used among adolescents and young adults, like other meningococcal vaccines.

By Brook Gould, PharmD Candidate

REFERENCES:

Continued on Page 5
**Spritam® (IR Levetiracetam) 3-D Printed Tablets**

Spritam® is a novel delivery form of oral levetiracetam.¹,² Spritam® is a three-dimensionally printed (3DP) tablet designed for patients who experience difficulty with swallowing. The 3DP tablet dissolves with just a small sip of water. Using the 3DP tablet eliminates the need to measure out accurate liquid doses of levetiracetam oral solution.¹,²

Spritam® bioequivalence was compared to available oral levetiracetam tablets in vitro only.³ Because Spritam® tablets met bioequivalence criteria set by the FDA and European Medicines Agency, in vivo testing was not required to gain approval of the product.³ No human studies with Spritam® have been published so no clinical data is available on the novel dosage form or its comparison to traditional levetiracetam tablets.

3DP levetiracetam tablets are available in 250 mg, 500 mg, 750 mg, and 1000 mg strengths.² The 3DP tablets should not be broken to administer a partial dose. Patients should be instructed to place the tablet in the mouth and take a sip of water. Once the tablet dissolves, in about 11 seconds, patients can swallow the spearmint-flavored medication.²

The maker of Spritam®, Aprecia Pharmaceuticals, developed the ZipDose® Technology 3DP method used to make Spritam®.¹ The company plans to use this technology to create other immediate-release medications, with an emphasis on those that work on the central nervous system. Aprecia Pharmaceuticals expects Spritam® to be available in early 2016.¹

**By Kaylyn DesRosier, PharmD Candidate**

**REFERENCES:**

