VOLUME 7, ISSUE 1

MARCH 2020

Drug and Poison Information Center Bulletin

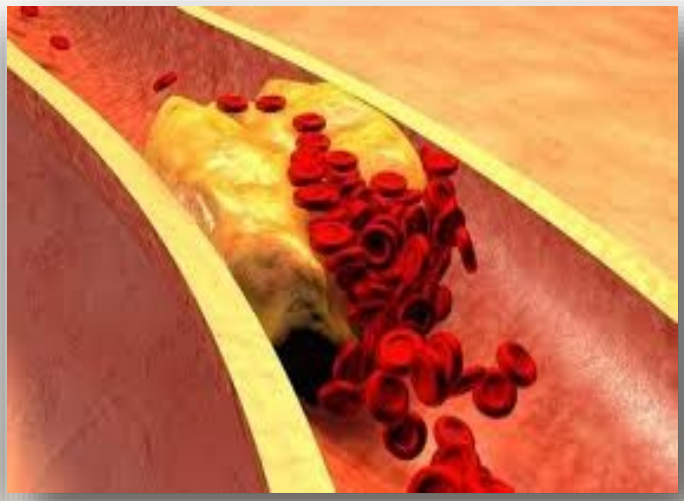
Faculty of Pharmacy

Tanta University

In this issue

New clinical trial for *Novel Corona Virus*

Valtoco….Diazepam Nasal Spray



New ADA guidelines

New drug approval for insomnia

NIH clinical trial of remdesivir to treat COVID-19

Study enrolling hospitalized adults with COVID-19 in Nebraska.

Till now, there are no specific therapeutics approved by the Food and Drug Administration (FDA) to treat people with COVID-19, the disease caused by the newly emergent SARS-CoV-2 virus (formerly known as 2019-nCoV). Infection can cause mild to severe respiratory illness, and symptoms can include fever, cough and shortness of breath. As of February 24, the World Health Organization (WHO) has reported 77,262 confirmed cases of COVID-19 and 2,595 deaths in China and 2,069 cases of COVID-19 and 23 deaths in 29 other countries. There have been 14 confirmed COVID-19 cases reported in the United States and an additional 39 cases among persons repatriated to the United states (U.S.) , according to the Centers for Disease Control and Prevention (CDC).

A randomized, controlled, double-blinded clinical trial to evaluate the safety and efficacy of the investigational antiviral remdesivir in hospitalized adults diagnose with coronavirus disease 2019 (COVID-19) has begun at the University of Nebraska Medical Center (UNMC) in Omaha. The first trial participant is an American who was repatriated after being quarantined on the Diamond Princess cruise ship that docked in Yokohama, Japan and volunteered to participate in the study. The study can be adapted to evaluated additional investigative treatments and to enroll participants at other sites in the U.S. and worldwide. **Remdesivir,** developed by Gilead Sciences Inc., is an investigational broad-spectrum antiviral treatment. It was previously tested in humans with Ebola virus disease and has shown promise in animal models for treating Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS), which are caused by other coronaviruses. Clinical trials of remdesivir are also ongoing in China. National Institute of Allergy and Infectious Diseases (NIAID) developed the current study taking those designs into account, and in accordance with consultations convened by the WHO on the development of a therapeutic trial for patients with COVID-19.

Inclusion criteria: Participants in the National Institute of Health (NIH)-sponsored trial must have laboratory-confirmed SARS-CoV-2 infection and evidence of lung involvement, including rattling sounds when breathing (rales) with a need for supplemental oxygen or abnormal chest X-rays, or illness requiring mechanical ventilation.

Exclusion criteria: Individuals with confirmed infection who have mild, cold-like symptoms or no apparent symptoms.

Method: All potential participants will undergo a baseline physical exam before receiving treatment. Participants in the investigational treatment group will receive 200 mg of remdesivir intravenously on the first day of enrollment to the study. They will receive another 100 mg each day for the duration of hospitalization, for up to 10 days total. The placebo group will receive, at an equal volume, a solution that resembles remdesivir but contains only inactive ingredients.

Clinicians will regularly monitor the participants and will assign their daily scores based on a predefined scale of clinical outcomes that considers factors such as temperature, blood pressure and use of supplemental oxygen, among others. Participants also will be asked to provide blood samples and nose and throat swabs approximately every two days. Researchers will test these specimens for SARS-CoV-2. Initially, investigators will compare participant outcomes on day 15 in both the remdesivir group and the placebo group to see if the investigational drug increased clinical benefit compared to placebo.

Outcome: A score on a seven-point scale ranging from fully recovered to death. Investigators will reevaluate this scale after reviewing data from the first 100 participants. An independent data and safety monitoring board (DSMB) will monitor ongoing results to ensure patient well-being and safety as well as study integrity. The DSMB will recommend the study be halted if there is clear and substantial evidence of a treatment difference between drug and placebo.

This trial is registered in **ClinicalTrials.gov** at search identifier **NCT04280705.**

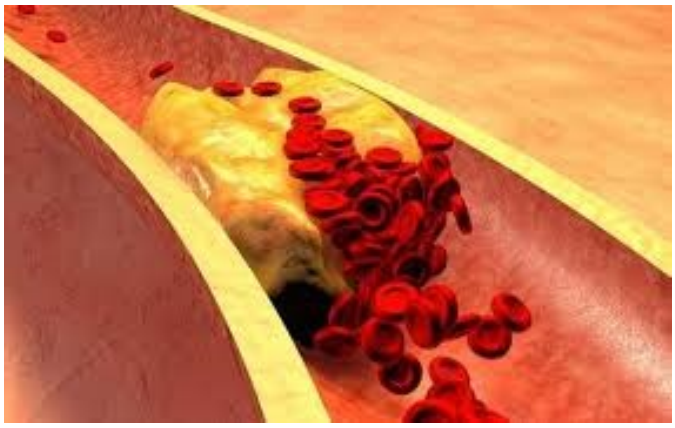
References:

- ***NIH clinical trial of remdesivir to treat COVID-19* begins. Available at: *https://www.nih.gov/news-events/news-releases/nih-clinical-trial-remdesivir-treat-covid-19-begins. Accessed in February, 2020.***
- ***Adaptive COVID-19 Treatment Trial, Available at: https://clinicaltrials.gov/ct2/show/results/NCT04280705?view=results. Accessed in March, 2020.***

By: Marwa EL-Sayed, PGCPD.

New recommendations in the updated 2020 American Diabetes Association (ADA) guidelines

Patients with type 2 diabetes have an increased prevalence of lipid abnormalities, contributing to their high risk of atherosclerotic cardiovascular disease (ASCVD). Multiple clinical trials have demonstrated the beneficial effects of statin therapy on ASCVD outcomes in subjects with and without coronary heart disease. Accordingly, all current diabetes guidelines strongly recommend using statin for all diabetic patients with ASCVD or 10-year ASCVD risk added to lifestyle therapy.



The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), a multicenter, randomized, double-blind, placebo-controlled trial, was designed to assess the long-term effect of icosapent ethyl (Vascepa®) on major adverse cardiovascular events (MACE). The trial enrolled 8,179 adults receiving statin therapy with moderately elevated triglycerides (135–499 mg/dL) and either established cardiovascular disease or diabetes plus at least one other cardiovascular risk factor who were randomized to icosapent ethyl 4 g/day versus placebo. Trial's findings were published in the New England Journal of Medicine (NEJM) in 2019, which demonstrated that:

- **25%** relative risk reduction (RRR) with P <0.001 for the primary end point composite of cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or unstable angina.
- **26%** reduction with P <0.001 in the composite of cardiovascular death, nonfatal MI, or nonfatal stroke.
- **Secondary end points** were significantly lower in the icosapent ethyl group than in the placebo group as illustrated in **Fig.1.**

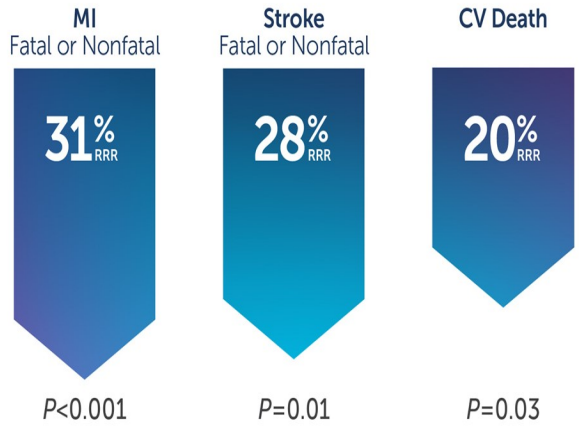


Fig.1. Significant reductions across secondary endpoints with VASCEPA.

Study adverse events:

The proportions of patients experiencing adverse events and were similar between both groups. While, the rate of atrial fibrillation and its risk requiring hospitalization in addition to the rate of peripheral edema were significantly higher in the treatment group than in the placebo group.

On the opposite side, the rate of anemia, diarrhea, and gastrointestinal adverse events were significantly lower in the icosapent ethyl group than in the placebo group.

Based on findings from this trial, an additional recommendation has been officially added to the section "Treatment of Other Lipoprotein Fractions or Targets" in the updated 2020 American diabetes Association guidelines follows:

In patients with ASCVD or other cardiac risk factors on a statin with controlled low density lipoprotein cholesterol (LDL-C), but elevated triglycerides (135-499), the addition of icosapent ethyl should be considered to reduce cardiovascular risk.

References:

- *Vascepa, Unprecedented CV risk reduction. Available at: https://www.vascepahcp.com/vascepa-efficacy/reduce-it/. Accessed in January, 2020.*
- *Vascepa Approval History. Available at: https://www.drugs.com/history/vascepa.html. Accessed in January , 2020.*
- *American Diabetes Association. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020; 43 (Suppl. 1): S135-S151.*
- *Bhatt DL, Steg PG, Miller M. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019;380(1):11-22.*

By: Bassant Maher, M.SC.

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Diazepam nasal spray as: Seizure rescue.

The (FDA) has announced the approval of **Valtoco**, diazepam nasal spray for the treatment of seizure clusters in patients with a history of epilepsy aged 6 years and above. These clusters are a form of seizures that start and stop. They occur in clusters or groups with one episode right after another. The FDA approved the formulation of this nasal spray as a rescue treatment for patients with epilepsy aged 6 years and above according to Neurelia-neuroscience base pharmaceutical company.

⇒ Clinical Data:

Valtoco was approved after evaluating the safety and efficacy of the nasal spray based on the results of a clinical trial that was conducted on 130 patients aged 6 years and above who successfully underwent treatment for more than 2,000 seizure clusters with diazepam nasal spray.

⇒ Safety issues:

Generally, the drug was found to be safe and well-tolerated. Some of the most common side effects of Valtoco were: headaches, nasal discomfort, and sleepiness. However, the FDA recommended that it should not be used for more than one seizure episode every 5 days and more than 5 episodes per month.

⇒ Dosage recommendations:

Valtoco is a ready-to-use nasal spray device available in 5 mg, 7.5 mg, and 10 mg strengths. Dosing is weight- and age-based if needed, patients can have a second dose of Valtoco four hours after the initial dose. However, it should not be used more than twice for a single episode of seizure.

References:

- ***FDA Approves Valtoco. Available at: https://www.drugs.com/newdrugs/fda-approves-valtoco-diazepam-nasal-seizure-rescue-5141.html. Accessed in January, 2020.***
- ***FDA Clears First Nasal Spray for Cluster Seizures in Kids 6 Years and Older. Available at: https://www.medscape.com/viewarticle/923774. Accessed in January, 2020.***

By: Mai Mousa, PharmD.

A novel drug for the treatment of insomnia

Last December, the FDA approved **lemborexant,** which have the trade name **Dayvigo®,** for the treatment of insomnia in adults, characterized by difficulties with sleep onset and/or sleep maintenance.

It acts through antagonism of orexin receptors. The orexin neuropeptide signaling system plays a role in wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive.

The recommended dosage of lemborexant is 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening.

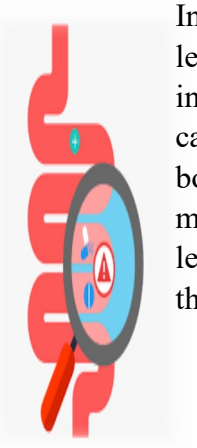
The dose may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability. Time to sleep onset may be delayed if taken with or soon after a meal.

⇒ Adverse effects:

The most common adverse reaction is "sleepiness" or "drowsiness", other adverse effects include: Sleep paralysis and complex sleep behavior.

⇒ Drug interactions:

Lemborexant is metabolized by CYP3A4, and to a lesser extent by CYP3A5. Concomitant use with CYP3A inhibitor such as itraconazole, clarithromycin, fluconazole or verapamil, may increase the risk of lemborexant adverse reactions, thus avoiding this interaction is recommended.



In addition, concomitant use of lemborexant with CYP3A inducer such as rifampin, carbamazepine, St. John's wort, bosentan efavirenz, etravirine, or modafinil may reduce lemborexant efficacy, thus avoid this interaction.

⇒ Pharmacokinetics:

Absorption	Distribution	Metabolism	Excretion
The time to peak concentration (t_{max}) of lemborexant is approximately 1-3 hours.	The volume of distribution is 1970 L. Protein binding of lemborexant is approximately 94% in vitro.	Lemborexant is primarily metabolized by CYP3A4, and to a lesser extent by CYP3A5.	Following administration of an oral dose, 57.4% of the dose was recovered in the feces and 29.1% in the urine (<1% as unchanged).

⇒ Contraindications:

Lemborexant is contraindicated in patients with narcolepsy.

References:

- ***Dayvigo Label at Drugs@FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212028s000lbl.pdf. Accessed in January, 2020 .***
- ***lemborexant (Rx): Available at: https://reference.medscape.com/drug/dayvigo-lemborexant-1000347#5 . Accessed in December, 2019.***

By: Amr Noweir, B. Pharm.

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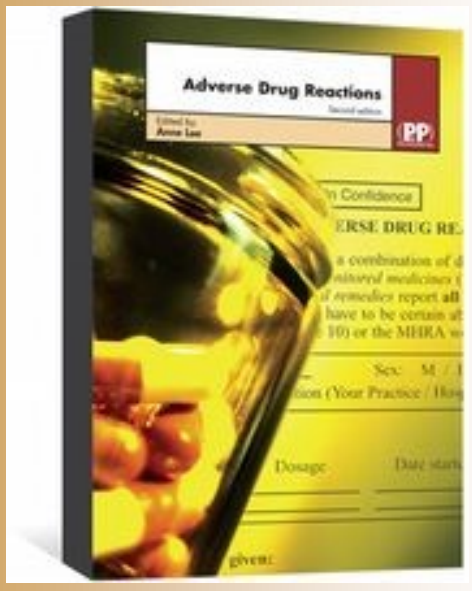
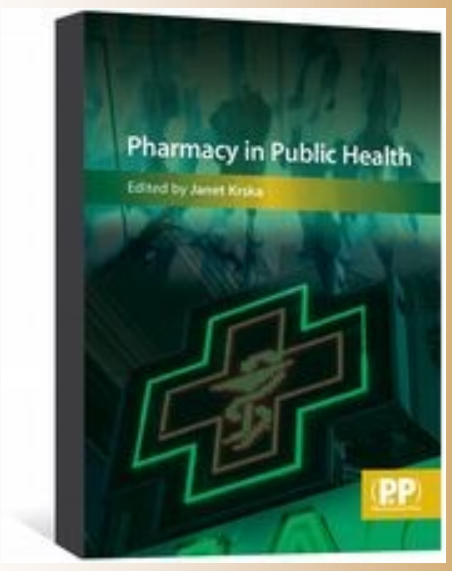


Adverse Drug Reactions



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Evidence-based online resources for COVID-19

COVID-19 Resource Centre: The LANCET:

- https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
- https://www.cell.com/2019-Ncov.
- https://www.elsevier.com/connect/coronavirus-information-center.

COVID-19 resources | Cochrane Library:

- https://www.cochranelibrary.com/collections/doi/SC000039/full.
- http://www.cochranelibrary.com/collections/doi/SC000040/full.
- https://www.cochranelibrary.com/collections/doi/SC000042/full.
- https://www.cochrane.org/news/cochranes-work-rapid-reviews-response-covid-19.
- https://www.cochranelibrary.com/about/cochrane-library-app.

Corona Virus Disease (COVID-19)-ASHP:

- https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx?la=en&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C.
- https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-Field-Surge-Hospital-ICU-Expansion-Response.ashx?la=en&hash=5EF2593AA435FABBEFE6E60BDB25DE6CCF7C9954.
- https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/Home-safety-recommendations_final.ashx?la=en&hash=0B930E050374284353FFE8BC28232BCCF12F71F2.
- https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP_COVID19_AssessmentTool.ashx?la=en&hash=D4222461335FCEAB8DE30F996388232700B9543F&hash=D4222461335FCEAB8DE30F996388232700B9543F.
- https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/Stewardship-of-Off-Label-Treatments.ashx?

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