ARCH
Annual Review of Changes in Healthcare

Novel Drug Review of Select Neurologic Drugs Approved in 2019

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Abstract

Each year, the Food and Drug Administration (FDA) releases a comprehensive list of all novel drugs approved throughout the year. The FDA's Center for Drug Evaluation and Research strives to approve new drugs to fill the gaps in healthcare of unmet needs of patients. This article focuses on select novel drugs approved in 2019, specifically for neurologic conditions. Drugs included are Cyplyta, a second-generation antipsychotic used in the maintenance of schizophrenia; Ubrelvy, a CGRP antagonist used for acute migraine attacks; Zulresso, the first drug treatment indicated for postpartum depression; and Wakix, the first noncontrolled treatment for excessive daytime sleepiness in narcoleptic patients.

Each year the Food and Drug Administration's Center for Drug Evaluation and Research develops a report including novel drugs approved throughout the year.[1] These drugs are new and innovative drugs that have never been seen on the market before.[1] As healthcare is evolving, new drug approvals allow patients quality treatments and relief to symptoms of disease states that were previously unmet.[1] In 2019, 48 novel drugs were approved as either new molecular entities or biologics license application.[1]

Nearly 1 billion people in the world suffer from a neurologic condition.[2] These conditions range from migraines, Alzheimer's, Parkinson's and strokes to mental health disorders.[2] This article examines select drugs targeted toward specific neurologic conditions approved by the FDA in 2019.

Caplyta (lumateperone)

Schizophrenia is a severe, chronic disease effecting approximately 2.6 million adults in the United States.[3] Schizophrenia may be effectively treated, however noncompliance among patients is common due to factors of unintentional nonadherence as a result of distressing medication side effects.[4] Schizophrenia treatment is extremely individualized and must consider how side effects, medication regimens, and drug-drug interactions will affect each patient to optimize their treatment.[4]

In response to the need for a diverse variety of antipsychotic medications, the FDA recently approved Caplyta.[5] Caplyta is a first-in-class drug which selectively modulates serotonin, dopamine, and glutamate receptors.[5-7] Several second-generation antipsychotics are known for their partial agonism of D2 receptors and inhibition of 5-HT2 receptors which help control positive symptoms in the mesolimbic and mesocorticol parts of the brain.[6,7] The advantage of Caplyta is the potential increase in phosphorylation at NMDA receptors.[7] This combination of pharmacologic actions may enhance sleep while decreasing aggression and agitation at lower doses. At higher doses, this combination may produce an antipsychotic and antidepressant effect.[5-7] Due to the drug's modulation of NMDA receptors, with further studies, researchers hope to prove Caplyta's ability to increase cognition as well.[7]

As with many antipsychotics, Caplyta carries a boxed warning for increased mortality in elderly patients with dementia-related psychosis.[5-7] Caplyta should not be used in patients with hematological disease or severe liver disease.[5,6] Patients should be monitored for tardive dyskinesias, hypotension, cognitive effects, and motor stability.[5,6] Patients with dysphagia, who are at risk for aspiration pneumonia or seizures should be closely monitored while taking Caplyta.[6]

Ubrelvy (ubrogepant)

Migraine is a debilitating condition which affects about 37 million people in the United States.[8] Recently, the FDA has approved, Ubrelvy, the first oral calcitonin gene-related peptide (CGRP) antagonist to diminish acute migraine attacks.[8-10] CGRP is distributed throughout the central nervous system, specifically in places involved in migraine pathophysiology.[10] During a migraine attack the blood vessels in the brain vasodilate due to an increase in CGRP.

Ubrelvy's main mechanism is to decrease CGRP to cause vasoconstriction.[10]

The effectiveness of Ubrelvy for the acute treatment of migraines was shown in two randomized, double-blind, placebo-controlled trials of 1,439 patients.[9] In this study patients who took Ubrelvy had a significant reduction in pain and migraine symptoms such as nausea and light or sound sensitivity when compared to the placebo.[9,10] Ubrelvy is contraindicated in concomitant use with strong CYP3A4 inhibitors.[8-10] A patient should not use Ubrelvy if he/she has severe renal impairment (CrCl <15 mL/min) or severe hepatic impairment.[10] Side effects of this medication include nausea, dry mouth, and sedation.[9,10]

Zulresso (brexanolone)

In the United State alone approximately 1 in 7 women will experience postpartum depression (PPD) within the first year after giving birth.[11,12] PPD is a serious mood disorder causing delusions, hallucinations, and depression that does not pass with time.[11] In the US about 4 million births occur each year, leaving approximately 600,000 PPD patients in danger of harming themselves.[12] This year the FDA approved the first drug specifically indicated for PPD, Zulresso.[13] The mechanism of Zulresso is not fully known, but is thought to be related to a positive allosteric modulation of GABA-A receptors.[13,14] During the third trimester, an endogenous steroid hormone called allopregnanolone peaks then rapidly declines after birth leading to major depressive symptoms and potentially PPD.[14] Zulresso works as an analog of allopregnanolone which modulates GABA-A receptors.[14]

Zulresso's efficacy is shown through a meta-analysis comparing 3 RCTs (n=267). 77.9% of patients responded and 50.7% remitted on Zulresso infusion compared to the 55.3% and 24.0% on placebo.[15] Zulresso is given over a 60-hour infusion in an inpatient setting.[13-15] The patient must be monitored for loss of consciousness, decreased breathing, and worsening of depressive symptoms.[14,15] Zulresso should not be used in patients with renal impairment.[14] Patients must be enrolled in the Zulresso REMS program in order to receive treatment.[13-15]

Wakix (pitolisant)

Narcolepsy is a neurologic disease which severely decreases a patient's quality of life with excessive daytime sleepiness (EDS) and sudden loss of muscle tone.[16] Several drug options may be used by patients to treat EDS, but these drugs have a high potential for abuse, tolerability, and adherence issues.[16] Wakix is a newly approved FDA medication which is a competitive antagonist and partial agonist at histamine H_3 receptors.[16,17] Although effective at the H_3 receptor, the medication has little effect on other receptors.[16] In preclinical trials Wakix showed increased wakefulness, decreased abuse potential, and no effects on pain threshold.[16] Wakix showed efficacy through a randomized control trial of 94 narcoleptic participants.[16] This study found Wakix is noninferior to the first line treatment for excessive daytime sleepiness, modafinil.[16] During this study cataplectic symptoms were significantly decreased compared to the placebo.[16] Modafinil failed to decrease cataplectic symptoms when compared to the placebo.[16] These results

suggest Wakix may be superior to modafinil in reducing cataplectic symptoms.[16] Wakix shows promising results, but needs future research to confirm benefits of long term use.

Wakix is the first drug for narcolepsy that is not a controlled substance.[16,18] Adverse effects include nausea, abdominal discomfort, decreased appetite, xerostomia, and weight gain.[16,18] Insomnia and decreased sleep quality may also be noted in these patients.[18] Wakix is contraindicated in patients with severe hepatic impairment or renal impairment (<15 mL/min).[18] Currently Wakix's is only available in a 35.6 mg oral form which is only indicated for excessive daytime sleepiness.[18]

Conclusion

Each year the FDA approves more drugs to benefit patients with unmet healthcare needs. This year a total of 48 novel drugs were released.[1] These drugs cover a range of disease states such as infection, psychiatric conditions, cardiac disease, endocrine disease, autoimmune disorders and more. Above are a few drugs covering neurologic disorders, but the FDA's comprehensive list is much more extensive than what is covered above. For a full list of the FDA's novel medications, please visit: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019

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