Acentra HEALTH

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2024 Quarter 4 Newsletter

FDA APPROVAL SPOTLIGHT

On June 26, 2024, a new therapy, Ohtuvayre (ensinfentrine) was approved for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adults. This treatment has a novel mechanism for this indication as an inhibitor of both the phosphodiesterase-3 (PDE-3) enzyme and the phosphodiesterase-4 (PDE-4) enzyme; this means that it blocks the hydrolyzation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), leading to the intracellular accumulation of these molecules.

Otuvayre is administered as a nebulization at 3 mg twice daily with no adjustment necessary for renal or hepatic impairment. Its main warning for use is that it may produce paradoxical bronchospasms, as well as it has an increased risk for psychiatric adverse reactions, including suicidality. However, it is overall well tolerated with the most common adverse drug events being back pain, hypertension, urinary tract infection, and diarrhea.

The ENHANCE-1 and ENHANCE-2 trials were randomized, placebo-controlled clinical trials that compared the efficacy of Ohtuvayre 3 mg twice daily to placebo as the change in baseline in FEV_1 $AUC_{0\text{-}12h}$ at week 12 in combination with other first-line maintenance therapies. In both of these trials, Ohtuvayre showed a statistically significant improvement in the least squares mean change from baseline in FEV_1 $AUC_{0\text{-}12h}$. Table 1 includes all relevant primary outcomes.

Additionally, Ohtuvayre showed mixed results for its impact on quality of life, as identified by administration of the St. George's Respiratory Questionnaire (SGRQ). After 24 weeks in the ENHANCE-1 trial, the SGRQ's responder rate was 58.2% for Ohtuvayre and 45.9% for placebo [odds ratio: 1.49; 95% CI (1.07, 2.07)]. After 24 weeks in the ENHANCE-2 trial, the SGRQ's responder rate was 45.4% for Ohtuvayre and 50.3% for placebo [odds ratio: 0.92; 95% CI (0.66, 1.29)]. However, it was well tolerated with similar rates of adverse drug events, as mentioned previously, in both ENHANCE-1 and ENHANCE-2.

Currently, the 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend either single or dual long-acting bronchodilator therapy as first-line maintenance COPD treatment, depending on the severity. There are no other therapies with phosphodiesterase activity that are currently approved for COPD. However, the GOLD guidelines do highlight the necessity for a more aggressive approach to therapy in patients with uncontrolled COPD.

Table 1: ENHANCE-1 and ENHANCE-2 Primary Outcomes

	ENHANCE-1		ENHANCE-2	
	Ohtuvayre (N=479)	Placebo (N=284)	Ohtuvayre (N=499)	Placebo (N=291)
N	477	282	498	291
LS Mean (95% CI)	61 (25, 97)	-26 (-64, 13)	48 (30, 66)	-46 (-70, -22)
LS Mean Difference from Placebo (95% CI)	87 (55, 118)	-	94 (65, 124)	-
P-Value	<0.0001	-	<0.0001	-

Due to its different administration (nebulization compared to other hand-held inhalers), likely high cost, unique mechanism of action, and lack of comparator studies with other established COPD maintenance treatments, it is unclear what the exact role of Ohtuvayre will be in the larger space of COPD treatments. For patient outcomes, increasing maintenance therapy options and improving the quality of literature and end evidence for COPD is a step in the right direction

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2024 GUIDELINE UPDATES

The American Gastroenterological Association (AGA) recent published a clinical practice update on the management of iron deficiency anemia in August 2024. The most recent guidelines for the management of iron deficiency anemia prior to this were published by the AGA in 2020. However, these were mostly focused on the gastrointestinal evaluation of this disease state, instead of treatment.

The World Health Organization (WHO) estimates that 30% of the world's population is affected by iron deficiency. This common disease state is caused by bleeding, insufficient iron intake, and decreased iron absorption. It can cause a plethora of signs and symptoms, such as pallor, fatigue, generalized weakness, headache, sore tongue, brittle nails, hair loss, etc.
Based on a robust literature search, the AGA formed fifteen best practice advices on the management of iron deficiency anemia. They are not listed in any particular order of importance, nor do they have specific ratings on the strength of evidence. These best practice advices are listed below.

1.) No single formulation of oral iron has any advantages over any other. Ferrous sulfate is preferred as the least expensive iron formulation.
2.) Give oral iron once a day at most. Every-other-day iron dosing may be better tolerated for some patients with similar or equal rates of iron absorption as daily dosing.
3.) Add vitamin C to oral iron supplementation to improve absorption.
4.) Intravenous iron should be used if the patient does not tolerate oral iron, ferritin levels do not improve with a trial of oral iron, or the patient has a condition in which oral iron is not likely to be absorbed.
5.) Intravenous iron formulations that can replace iron deficits with 1 or 2 infusions are preferred over those that require more than 2 infusions.
6.) All intravenous iron formulations have similar risks; true anaphylaxis is very rare. The vast majority of reactions to intravenous iron are complement activation–related pseudo-allergy (infusion reactions) and should be treated as such.
7.) Intravenous iron therapy should be used in individuals who have undergone bariatric procedures, particularly those that are likely to disrupt normal duodenal iron absorption, and have iron-deficiency anemia with no identifiable source of chronic gastrointestinal blood loss.
8.) In individuals with inflammatory bowel disease and iron-deficiency anemia, clinicians first should determine whether iron-deficiency anemia is owing to inadequate intake or absorption, or loss of iron, typically from gastrointestinal bleeding. Active inflammation should be treated effectively to enhance iron absorption or reduce iron depletion.
9.) Intravenous iron therapy should be given in individuals with inflammatory bowel disease, iron-deficiency anemia, and active inflammation with compromised absorption.

10.)In individuals with portal hypertensive gastropathy and iron-deficiency anemia, oral iron supplements initially should be used to replenish iron stores. Intravenous iron therapy should be used in patients with ongoing bleeding who do not respond to oral iron therapy.
11.)In individuals with portal hypertensive gastropathy and iron-deficiency anemia without another identified source of chronic blood loss, treatment of portal hypertension with nonselective β-blockers can be considered.
12.)In individuals with iron-deficiency anemia secondary to gastric antral vascular ectasia who have an inadequate response to iron replacement, consider endoscopic therapy with endoscopic band ligation or thermal methods such as argon plasma coagulation.
13.)In patients with iron-deficiency anemia and celiac disease, ensure adherence to a gluten-free diet to improve iron absorption. Consider oral iron supplementation based on the severity of iron deficiency and patient tolerance, followed by intravenous iron therapy if iron stores do not improve.
14.)Deep enteroscopy performed in patients with iron-deficiency anemia suspected to have small-bowel bleeding angioectasias should be performed with a distal attachment to improve detection and facilitate treatment. Small-bowel angioectasias may be treated with ablative thermal therapies such as argon plasma coagulation or with mechanical methods such as hemostatic clips.
15.)Endoscopic treatment of angioectasias should be accompanied with iron replacement. Medical therapy for small-bowel angioectasias should be reserved for compassionate treatment in refractory cases when iron replacement and endoscopic therapy are ineffective.

In summary, for pharmacological therapy, the recommendations emphasize daily oral iron and vitamin C as the first-line therapy for iron deficiency anemia. If oral iron is not tolerated or the patient's anemia or comorbidities are too severe to make oral iron practical, intravenous iron in 1-2 infusions is recommended as a second-line treatment option. Additionally, it is important to note the emphasis placed on identifying and treating any underlying pathologies that may cause or exacerbate iron-deficiency anemia.

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LEGISLATIVE NEWS

As legislation on the topic of pharmacy benefit managers (PBMs) have become more common and more popular, a recent bill called the Ensuring PBM Competition Act was introduced to the House on December 15, 2023 and referred to the Subcommittee on Health as of December 17, 2024. This legislation seeks “to amend title XVIII of the Social Security Act to prohibit the Secretary of Health and Human Services from entering into contracts with PDP sponsors of prescription drug plans that have a contract with certain pharmacy benefits managers.”

The purpose of this bill is essentially to prevent conflicts of interest within the federal government, specifically any party that effects legislation or management of healthcare. Any PBMs that participate in Medicare are not allowed to own a pharmacy. With the large majority of PBM market participants being controlled by a handful of PBM entities, competition in the market is severely limited.

This means that pharmacies not in relationships with the major PBMs have trouble competing for adequate reimbursement. Additionally, PBMs may directly control or own other entities withing the system, such as online pharmacies. Therefore, this legislation would hopefully improve outcomes for smaller, locally-owned pharmacies and therefore improve access in rural communities and drug copays overall. This could in turn improve patient outcomes by ensuring that each patient is able to easily access all need prescription drugs without exorbitant costs.

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