Take 3 – Practical Practice Pointers© November 5, 2018 Edition

Xofluza for Flu, Epilepsy Society Choosing Wisely, Grief

From the FDA

1) New Influenza Anti-Viral Medication Approved by FDA

On October 24th the Food and Drug Administration approved baloxavir marboxil (Xofluza) for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

This the first new antiviral influenza treatment with a novel mechanism of action approved by the FDA in nearly 20 years. The safety and efficacy of Xofluza, which is taken as a single oral dose, was demonstrated in two randomized controlled clinical trials of 1,832 patients where participants were assigned to receive either Xofluza, a placebo, or another antiviral flu treatment within 48 hours of experiencing flu symptoms. In both trials, otherwise healthy patients had a shorter time to alleviation of symptoms compared with patients who took the placebo (approximately 24 hours – comparable to oseltamivar) and there was a decreased length of time of viral shedding and levels of virus in the nose and throat compared with placebo or oseltamivir at 24 hours post treatment. Unlike neuraminidase inhibitors, such as oseltamivir (Tamiflu), which inhibit the action of neuraminidase, baloxavir prevents replication by inhibiting cap-dependent endonuclease activity of the viral polymerase.

The most common adverse reactions in patients taking Xofluza included diarrhea and bronchitis.

In the announcement, FDA Commissioner Scott Gottlieb provided this reminder: "While there are several FDA-approved antiviral drugs to treat flu, they're not a substitute for yearly vaccination. Flu season is already well underway, and the CDC recommends getting vaccinated by the end of October, as seasonal flu vaccine is one of the most effective and safest ways to protect yourself, your family and your community from the flu and serious flu-related complications, which can result in hospitalizations."

According to Genentech, the product is expected to be available in the coming weeks. Xofluza will be supplied as 20mg and 40mg tablets. Price has not been announced.

My Comment:
This certainly provides another important option for influenza treatment. More information will be shared as it becomes available. Interestingly, the lead author was on faculty at the University of Virginia when I was a medical student and resident there, and is still there on faculty.

References:
FDA News Release October 24, 2018: Announcement
Hayden F, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med September 6, 2018; 379:913-923. Article

From the Choosing Wisely Campaign

2) New Recommendations From the American Epilepsy Society

Avoid routine testing for antiepileptic drug (AED) levels in people with epilepsy: AED level testing should not be routinely ordered when seizures are well controlled, and no adverse effect is suspected. The reference ranges should not be used as a rigid framework. The effectiveness and tolerability of treatments should be determined by the clinical responses. AED levels should be ordered to address a specific question. Some examples include weight-based dosing adjustments in young children, adherence, suspected toxicity, and pregnant women.

Do not routinely order electroencephalogram (EEG) as part of initial syncope work-up: EEG will be negative in a large portion of patients with epilepsy, and may be positive in patients without epilepsy. False positive EEG findings commonly lead to unnecessary use of antiepileptic drugs and may delay the syncope diagnosis and treatment. EEGs are most helpful in specific situations when there is high pre-test probability for epilepsy based on history and exam, and clinical presentation.

Do not prescribe long-term treatment with antiepileptic drugs after withdrawal seizures: Alcohol and other withdrawal seizures occur due to abrupt cessation in a person who is substance-dependent, and can usually be readily identified by the clinical scenario. Once the acute detoxification is complete, anti-epileptic drugs are not indicated. It is, however, important to identify scenarios where there is increased risk of epilepsy, such as prior epilepsy diagnosis, acute intoxication related brain injury, and seizures with history of alcohol use but without acute withdrawal.

My Comment:
I found these 3 recommendations to be good reminders, particularly as many of us likely care for some patients who have seizure disorders. The 1st recommendation was of particular interest, as most neurologists I work with still order yearly drug levels. There may be other reasons for doing so, including medical-legal ones, but it makes sense that therapeutic decisions are not commonly made from these “routine” levels.

Reference:
Choosing Wisely August 15, 2018. Link

From the Literature

3) The Relationship of Grief, Premature Mortality, and Inflammation

Grief for another is conceptualized by strong negative emotions, which include longing, sadness, and preoccupations with thoughts, recollections, and images of the one being grieved. In the initial months after the loss of a spouse, those who are widowed are at risk for cardiovascular problems and premature mortality. Indeed, "broken heart syndrome” or Takotsubo cardiomyopathy can cause short-term heart muscle failure which at times can be fatal. This phenomenon has been associated with pro-inflammatory markers and a surge of the stress hormone epinephrine in response to the stressful event.

Additionally, in the general population, depression is associated with chronic low-grade inflammation, a key predictor of cardiovascular problems, morbidity, and mortality. Although depression and grief share similarities, they are distinct constructs.

The intention of this study was to attempt to see if there might be a way to predict greater risk among the bereaved by measuring inflammatory markers. It also sought to determine if those who are widowed and already experiencing elevated levels of depressive symptoms compared with the general population had higher levels of inflammation compared with those who are widowed and report fewer depressive symptoms.

The study included 99 participants who had lost their spouse no later than 14 weeks prior to assessment. Participants must have been married to their partner for at least 3 years before the loss. This was because bereaved individuals are considered "fully attached" at this point, according to literature concerning adult attachment. The participants completed a blood draw and psychological assessments. Proinflammatory T cell-derived cytokines were assessed, which included interferon gamma (IFN-γ), interleukin (IL)-6, tumor necrosis factor alpha (TNF-α), IL17-A, and IL-2.

The authors found that bereaved individuals with a higher grief severity had higher levels of the proinflammatory cytokines IFN-γ, IL-6, and TNF-α than those with less grief severity. Those who experienced higher levels of depression exhibited elevated levels of proinflammatory cytokines compared with those who had lower levels of depression.

This is the first study to demonstrate a direct correlation between levels of inflammatory markers and grief severity as well as depression severity.

My Comment:
I suspect most readers have experienced the “heavy heart” of grief at some point in their lives. For most, this is a normal adaptive response to emotional intensity. This study supports the notion that in some this can be associated with higher inflammation that may place them at risk for increased morbidity and mortality. The next research question would be to see if certain interventions to lower inflammation (both through lifestyle interventions and pharmacologic interventions) might have an impact on this risk. In the meantime, considering how we might identify those at increased risk based on medical history and having a lower threshold for intervention seems a reasonable response to this disease-oriented evidence.

As someone who has become a “student” of physician distress over the last 2 decades, I found myself reflecting as to how I recognize and process grief, not simply in my personal life, but in my professional life as well. In the work we do, being in situations that may catalyze at least a low level of grief for others and their suffering happens regularly. Seems like something worth pondering (see the “4th Aim Pause” for this week).

Reference:
Fagundes C et al. Grief, depressive symptoms, and inflammation in the spousally bereaved. *Psychoneuroendocrinol*. Published online October 11, 2018. Abstract

Feel free to forward Take 3 to your colleagues. Glad to add them to the distribution list.

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