Pharmacology Watch

Evidence-based updates in clinical pharmacology

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Researchers Offer Remedies for FDA's Accelerated Approval Program

A provocative piece recently published in the *New England Journal of Medicine* focused on the cost of new drugs that are approved under the FDA's accelerated approval program. The program allows drugs to be approved based on surrogate endpoints that are "reasonably likely to predict clinical benefit," and now represents about 10% of all new drug approvals. The surrogate endpoints often are a biomarker or functional endpoint, but approval comes with the requirement that the manufacturer conduct postapproval trials to confirm the drug's efficacy for the approved indication. But once approved, manufacturers are free to charge consumers and insurers whatever they believe the market will bear. In the case of eteplirsen, approved for the treatment of muscular dystrophy, the cost is $300,000 per year. That price comes without evidence that the drug affects disease progression.

The authors suggested several remedies. Manufacturers could be required to offer additional price concessions to public insurance programs until confirmatory trials are completed. They also suggested that the FDA do more to ensure that confirmatory trials are conducted in a timely fashion after accelerated approval. Lastly, the authors recommended that drugs approved under the accelerated approval program with a cost above a certain threshold (such as $100,000 per year) be the subject of formal economic impact analyses after one to two years on the market (*N Engl J Med* 2017;376:2001-2004). The FDA's new commissioner, Scott Gottlieb, MD, has promised to ease regulations to make sure that drugs reach the market more quickly. Dr. Gottlieb has worked at the FDA in other capacities and also has served on the boards of several pharmaceutical companies.

Investigators Conclude Long-term Opioid Use Increases Dependency and Overdose Risks

The opioid epidemic has raised questions regarding the long-term use of opioids for chronic pain conditions. The authors of a new study looked at the utility of long-term opioids in patients with polyneuropathy, one of the most common painful conditions managed in general practice.

Nearly 2,900 patients with polyneuropathy were assessed in a retrospective, population-based, cohort study to assess opioid prevalence as well as functional status and adverse outcomes. Patients with polyneuropathy who were receiving long-term opioids exhibited multiple functional status markers that were modestly poorer even after adjusting for medical comorbidity, including increased reliance on gait aids (odds ratio, 1.9; 95% confidence interval, 1.4-2.6). No functional status markers were improved by long-term use of opioids, while adverse outcomes were more common, including depression (adjusted hazard ratio [HR], 1.53), opioid dependence (HR, 2.85), and opioid overdose (HR, 5.12). The authors concluded that "long-term opioid therapy did not improve functional status but rather was associated with a higher risk of subsequent opioid dependency

and overdose" (*JAMA Neurol*. Published online May 22, 2017. doi:10.1001/jamaneurol.2017.0486).

An accompanying editorial noted that lack of evidence for benefit from long-term opioid use and accumulating evidence of harm has prompted the CDC to publish new guidelines recommending that opioids not be used as first-line treatment agents for the management of chronic pain, and if used, opioids only should be used as an adjunct to a comprehensive pain management program (*JAMA Neurol*. Published online May 22, 2017. doi:10.1001/jamaneurol.2017.0466).

Ohio Attorney General Files Suit Against 5 Pharmaceutical Companies Over Opioids

In related news, the Ohio attorney general filed a lawsuit against five opioid manufacturers, alleging fraudulent marketing that misled the state, prescribers, and patients about the risks of these medications. Ohio has been hit particularly hard by the opioid epidemic, with thousands of prescription overdose deaths in recent years. The suit was filed against Purdue Pharma, Endo Health Solutions, Teva Pharmaceutical (and its subsidiary Cephalon), Johnson & Johnson (and its subsidiary Janssen Pharmaceuticals), and Allergan. In particular, Purdue has been criticized for its marketing of OxyContin, which included funding patient advocacy groups to lobby for wider treatment of pain.

Up to one-third of Ohio residents have been prescribed an opioid, according to the suit. This is the second lawsuit filed by one of the hard-hit states, following Mississippi, with other states expected to follow suit.

FDA Actions

The FDA has approved edaravone for the treatment of amyotrophic lateral sclerosis (ALS), the first new treatment for ALS in more than 20 years. The drug is a potent radical scavenger, which was developed in Japan to treat acute cerebral embolism. Efficacy for ALS was shown in 137 patients given edaravone or placebo; edaravone-treated patients showed modest improvement in the ALS functional rating scale up to week 24. The drug is given as an IV infusion daily for 14 days, followed by a 14-day drug-free period, then for 10 days every 28 days. The cost is $1,000 per daily dose. Edaravone was approved with orphan designation and will be marketed starting in August as Radicava.

The FDA has expanded the indication for the checkpoint inhibitor pembrolizumab (Keytruda) to include all solid tumors with a specific biomarker, the first time the agency has approved a cancer treatment based on a biomarker rather than the location in the body where the tumor originated. Checkpoint inhibitors, including pembrolizumab, target the programmed cell death 1 (PD-1/PD-L1) receptor on cancer cells. The specific biomarker covered under this new approval is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). With the new approval, pembrolizumab is approved for adult and pediatric patients with unresectable or metastatic solid tumors, most commonly colorectal, endometrial, and gastrointestinal cancers, but also less frequently in breast, prostate, bladder, thyroid gland, and others. The accelerated approval was based on data from 149 patients with MSI-H or dMMR cancers enrolled across five single-arm clinical trials. Pembrolizumab previously was approved for certain patients with metastatic melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head and neck cancer, refractory classical Hodgkin lymphoma, and urothelial carcinoma.

The FDA has expanded the indication for tocilizumab to include giant cell arteritis (GCA). The drug is an interleukin-6 receptor antagonist that previously was approved for rheumatoid arthritis. It is given as a weekly subcutaneous injection. Efficacy and safety were shown in a study of 251 patients with GCA treated with tocilizumab plus prednisone vs. prednisone plus placebo, in which combination therapy resulted in a higher number of patients with sustained remission. The drug carries a boxed warning regarding severe infections. Tocilizumab was granted breakthrough therapy designation and given a priority review. It is marketed as Actemra.

The FDA has approved the first generic version of the attention-deficit/hyperactivity disorder (ADHD) drug atomoxetine (Strattera). Four manufacturers are ready to start production immediately. Atomoxetine is approved for the treatment of ADHD in pediatric and adult patients. Like other ADHD medications, atomoxetine carries a boxed warning for the increased risk of suicidal ideation in children and adolescents. ■

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