DRUGMonitor

Brief summaries of recent drug approvals, interactions, and adverse events

A Puzzling Plus to Placebo Adherence

Some women in the Heart and Estrogen/Progestin Replacement Study (HERS) had a 48% lower risk of dying. Why? Because they were very adherent to their *placebo*.

In HERS, 1,375 women were randomly assigned to placebo; of those, 1,290 took their prescribed study "medication" at least 75% of the time. When the more-adherent group was compared with the less-adherent group, differences showed in nearly every studied outcome: total mortality (8% vs 15%, respectively), cardiovascular disease mortality (5% vs 7%), noncardiovascular disease mortality (3% vs 8%), coronary artery disease (CAD) mortality (4% vs 7%), and incident cancer (6% vs 13%). In the remaining category—incident CAD events—the 2 groups were the same (13%).

Placebo in itself doesn't reduce mortality, but perhaps the type of person who takes all her medicine is different in other ways from someone who does not. For example, is she more likely to take other life-prolonging medications? Older data suggest this is unlikely, the researchers say. Is she more likely to engage in a healthy lifestyle? Unfortunately, HERS was limited on the topic of many important lifestyle covariates, such as daily exercise, self-perceived well-being, and psychosocial measures.

Did some patients develop illnesses with a prodrome (such as cancer), which could be responsible for both the death and a reduction in adherence to the study medication? The association of higher adherence with reduced mortality was markedly attenuated when the researchers took out the last 1 or 2 adherence measurements closest to death.

Still, their findings lead to other questions that should be examined more fully in analyses, the researchers advise, as well as in prospective studies.

Source: Padula AM, Pressman AR, Vittinghoff E, et al. *Am J Med.* 2012;125(8):804-810. doi: 10.1016/j.amjmed.2012.02.014.

Parkinson Disease Medication Adverse Effect: A Camera Museum

If a patient with Parkinson disease (PD) begins behaving unusually, even bizarrely, double-check the dopaminergic drugs, suggest physicians from the University of Erlangen in Erlangen, Germany.

The authors note that drug-associated impulse control disorders and other psychiatric symptoms, such as delusions, are well known.

They report on the case of a patient who coped with worsening symptoms on his own by gradually increasing his PD medication. Around that time he suddenly decided to open a camera museum and began buying cameras. He also began contacting women might model for nude photography and started a romantic relationship with one. His seemingly abrupt detour into obsessive and compulsive behavior led to his being admitted to an inpatient service for reevaluation.

Except for the PD, diagnosed 6 years before, his medical history was unremarkable. Psychiatric examination revealed no hallucinations, delirium, or other acute brain dysfunction. He had no history of drug abuse.

Before his admission he was taking up to 90 mg ropinirole and 900 mg/225 mg levodopa/benserazide per day, as well as 300 mg amantadine and 1 mg rasagiline per day. The physicians treated him first by gradually reducing the levodopa and ropinirole. His motor function—the reason he began upping his dosage in the first place—did not worsen. Soon, he began to realize what he'd been doing for 4 months and became aware of the financial consequences. He also no longer wanted to continue his recent relationship. Consequently, he became clinically depressed and was then admitted to a psychiatric ward. Antidepressive treatment and counseling helped the depression resolve after 3 weeks.

The authors note that drug-associated impulse control disorders and other psychiatric symptoms, such as delusions, are well known. They also point out that the drugs used to treat PD can cause psychiatric symptoms, in most cases short lived. However, they add, less is known about more complex regimens that include both short- and long-acting dopaminergic drugs. The "long-lasting, rare, and confusing symptom complex" observed in their patient, they say, exceeds the usual profile seen in patients with PD and might be due to cumulative effects caused by chronically elevated plasma levels enhanced by peaking levels.

Their patient could easily have been misdiagnosed as having a genuine psychiatric disease,

the researchers say. They add that specialists and primary care clinicians need to be aware that adverse symptoms such as their patient's could appear even in patients treated with lower doses of dopaminergic drugs.

Source: Müller H, Knossolla F, Breuer L, Kornhuber J, Marquardt L. *Am J Med.* 2012;125(8):e3. doi: 10.1016/j.amjmed.2012.01.031.

Antibiotics May Work Best for Enterohemorrhagic *E coli*–Induced Hemolytic Uremic Syndrome

It may be time to rethink current treatment recommendations for adults with hemolytic uremic syndrome (HUS), say researchers for the EHEC-HUS consortium who conducted a multihospital study of patients involved in an outbreak of enterohemorrhagic *Escherichia coli*. Their findings upended some assumptions and reestablished others.

In northern Germany in 2011, 3,842 people were infected with enterohemorrhagic *E coli*, the largest outbreak to date. Of those, 855 developed HUS. In a second, smaller outbreak in Scotland, 34 of 512 people infected with enterohemorrhagic *E coli* O157:H7 developed HUS.

The large number of patients and the differences in treatment strategies afforded researchers the perfect opportunity to compare and contrast the main standard treatments—plasmapheresis, glucocorticoids, antibiotics, and eculizumab.

The researchers evaluated the effectiveness of the treatments in 298 patients. In nearly all cases, diarrhea turned sanguineous within 1 day and lasted a median of 6 days. Most patients were admitted to the hospital within 7 days after the onset of diarrhea. The median length of hospital stay was 19 days.

More than half of the patients temporarily needed dialysis; 3 needed long-term treatment. Thirty-seven patients had seizures, 54 required mechanical ventilation, and 12 died.

Plasmapheresis was the primary choice, used to treat 251 patients. Most of the centers also used high-dose prednisone or prednisolone as premedication before fresh frozen plasma. However, 7 centers, with 80 patients, did not administer glucocorticoids.

Antibiotic treatment in these cases is controversial, the researchers say, because theoretically they could cause an intestinal Jarisch-Herxheimer reaction, releasing Shiga toxin through bacterial death. Still, 1 university hospital administered a combination of at least 2 antibiotics.

Sixty-seven patients received eculizumab, a monoclonal antibody that has been used successfully to treat patients with paroxysmal nocturnal hemoglobinuria and atypical HUS. At the beginning of the German outbreak, it was reported that eculizumab seemed to be beneficial in 3 infants with severe Shiga toxin–associated HUS, and it had been used as a compassionate treatment for HUS thereafter.

The researchers found no clear benefit from plasmapheresis, with or without glucocorticoids. They also found no short-term benefit for eculizumab: Patients still developed new complications, such as a seizure or the need for ventilation. In more than 40% of the cases, plasmapheresis was continued after eculizumab had been started. However, the effect of eculizumab may have been confounded by the fact that the patients may have been sicker. What's more, nearly all patients on the drug were also being treated with azithromycin for meningococcal prophylaxis.

However, aggressive antibiotic treatment (that is, at least 2 antibiotics) had "encouraging" results, the researchers found. Not only was enterohemorrhagic *E coli* eradicated about 8 days sooner than with the other treatments, but the patients had significantly fewer seizures (2% vs 14% with plasmapheresis), required no abdominal surgery, and showed no signs of toxic shock. Moreover, no patients given antibiotics died compared with 8 on plasmapheresis and 3 on eculizumab. The researchers suggest that antibiotics are beneficial in the later stages of the disease when the prodromal phase with diarrhea has nearly subsided.

Source: Menne J, Nitschke M, Stingele R, et al. *BMJ.* 2012;345:e4565. doi: 10.1136/bmj.e4565.

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