DRUGMonitor

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

Lithium: A Standby With Unsuspected Benefits?

Patients with mood disorders are at high risk for suicide—their risk is as much as 30 times higher than that of the general population, say researchers from the University of Verona in Italy and the University of Oxford in the United Kingdom. Medication plays a relatively minor role in most suicide prevention strategies, they add, but that role may have been underestimated. Having previously reported in 2005 on the benefits of long-term lithium in reducing the risk of suicide in patients with mood disorders, they decided to update their meta-analysis. Their findings indicated that there is still a place for long-term lithium and that its antisuicidal effects may actually be greater than the effect on mood episodes.

The researchers reviewed 48 studies, including 8 that contributed new data. Nearly half the studies compared lithium with a placebo, but lithium was also compared with 14 other treatments, including amitriptyline, carbamazepine, valproate, and fluoxetine. Follow-up ranged from 4 months to 48 months. Overall, 6,674 patients were randomized to one of the active agents or placebo.

Lithium was associated with reducing the risk of death and suicide by > 60% compared with placebo. The consistency of results across studies, the researchers say, may indicate that lithium's life-preserving effect is independent of the comparator. They found no clear benefit, however, for lithium compared with placebo in preventing deliberate self-harm.

In unipolar depression, lithium was associated with a reduced risk of suicide and the number of total deaths compared with placebo. When lithium was compared with other drugs, a statistically significant difference was found only with carbamazepine for deliberate self-harm (odds ratio, 0.14; 95% confidence interval, 0.02-0.83), although lithium tended to be better than the other active comparators.

A new finding, the researchers say, is that lithium reduces the risk of suicide and total deaths in people with both unipolar and bipolar depressive disorder.

The reduction in risk of all-cause mortality mainly reflected a reduction in suicide. A "parsimonious" explanation for that, the researchers say, might be that lithium reduces the relapse of the mood disorder. However, they say, because lithium is not as potent in acute phase therapy as are other antidepressants (which in turn seem not to have similar antisuicidal effects), there could be something else at work, particularly since the antisuicidal effect in their analysis was larger than the effect on mood episodes. One mechanism might be that lithium reduces aggression and possibly impulsivity, both associated with an increased risk of suicide.

Lithium has adverse effects (likely dose related) that concern both patients and clinicians. The oral dose and plasma concentrations need to be monitored to ensure optimum efficacy and adequate tolerability. However, despite these drawbacks, the researchers say, a balanced view of the benefits and harm should take into account the fact that lithium can reduce deliberate self-harm in people with bipolar disorder and recurrent unipolar depression.

Source: Cipriani A, Hawton K, Stockton S, Geddes JR. *BMJ.* 2013;346:f3646. doi: 10.1136/bmj.f3646.

Guideline-Based Treatment Enhances Survival in the Oldest-Old

Guideline-based medications are still woefully underused in elderly patients, in part because until fairly recently, older patients were routinely excluded from clinical trials, making it hard to show benefits for them from any drug therapies. Studies have finally begun to include adults aged ≥ 65 years, but the oldest-old (aged ≥ 85 years) are still a relatively unknown quantity, even though they comprise the fastest-growing segment of the population. Researchers from the University of Massachusetts Medical School in Worcester, the Institute for Aging Research and Beth Israel Deaconess Medical Center, both in Boston, all in Massachusetts, though, offer a carefully structured argument for more guideline-based pharmacotherapy in the oldest patients.

Research had indicated that guideline-based pharmacotherapy was on the rise. Simultaneously, people were living longer after acute myocardial infarction (MI). But were the 2 facts linked? Using data from the Worcester Heart Attack Study, the researchers conducted a study of 1,137 patients aged 85 to 105 years, including 527 patients who were hospitalized with acute MI between 1997 and 2001 and 610 patients hospitalized between 2003 and 2007.

Those dates are important, because between 1997 and 2007, the average number of guideline-based medications administered during hospitalization for acute MI (eg, aspirin, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and lipid-lowering drugs) increased significantly from 2.3 to 3.4, and the average number prescribed at discharge increased

from 1.8 to 2.9 (both $P < .001$). The researchers also found corresponding trends for medications never prescribed. The proportion of patients who used aspirin during hospitalization only, without continuation at discharge, dropped from 30% to 17%.

When the researchers examined the possible mediating effect of guideline-based medications on 90-day survival, they found an encouraging trend: Mortality was significantly lower from 2003 to 2007 for the oldest-old, compared with 1997 to 2001, even after adjusting for comorbidities and medications (hazard ratio, 0.73). First, their step-by-step analysis revealed a significant relationship between time trend and mortality during the 90 days after acute MI. Second, their analysis showed significant increases in guideline-based medication use over the study period. Third, the unadjusted relationship of time trends with postdischarge survival improvements did not persist after adjustment for guideline-based medication use, supporting the argument, they say, that the use of guideline-based medications mediated observed survival trends.

Source: Tjia J, Allison J, Saczynski JS, et al. *Am J Med.* 2013;126(9):798-804.
doi: 10.1016/j.amjmed.2013.02.026.

VRE Transmission: What's Really Happening?

Vancomycin-resistant *Enterococci* (VRE) are a problem, but are they a problem for everyone? A 2-year study done at Heidelberg University Hospital, one of Germany's largest university hospitals, suggests that some patients are at a higher risk, but generally, the risk of transmission from bacteremic patients to hospitalized contacts is low.

During the study, 16,507 VRE screening tests were performed on 9,258 patients, showing an overall VRE prevalence of 6.1%, accounting for 256 patients in 2009 and 304 patients in 2010. The majority (93%) of all isolated VRE strains were *Enterococcus faecium* (*E faecium*); *Enterococcus faecalis* (*E faecalis*) accounted for 5.7%. High-level gentamicin resistance (HLGR) in *E faecium* and *E faecalis* were present in 147 of 552 isolates.

Of all VRE-positive screened patients, 72% were treated in an intensive care unit (ICU) or an intermediate care unit (IMC), and 44% were surgical patients. Ten of 142 wards accounted for 67% of all patients who were VRE-positive.

Only 19 of the 560 patients who were VRE-positive experienced VRE bacteremia during the study period. Four of the 19 patients who tested negative for VRE on admission tested positive after VRE bacteremia was found. Of the remaining 15 patients, 9 were colonized before VRE bacteremia occurred; 6 remained noncolonized. Among VRE-positive blood cultures, 58% were monomicrobial, 42% were polymicrobial, and HLGR was found in 32%.

The patients with bacteremia were in a multimorbid cohort with more risk factors, such as diarrhea, immunosuppressive drugs, antibiotics, and previous hospitalization, the researchers say. The patients were older, and many had underlying cancer. The majority had been previously treated in a hospital before admission to the study hospital; 74% were hospitalized in an ICU or IMC, and 32% were transplant patients.

All patients with bacteremia received systemic antibiotics during the hospital stay, and 42% received immunosuppressant drugs. Unfortunately, the researchers say, the data collected on specific antibiotics, such as vancomycin, were inadequately documented in 68% of cases and could not be included in the statistical analysis.

Mortality was high in these very ill patients (37%), and they had much longer hospital stays (mean of 52 days vs 32 days for those who survived).

The researchers identified 58 patients as contacts of VRE bacteremia patients. Of those 58, only 4 patients developed VRE colonization, based on screening results. Moreover, only 2 patients were colonized with a VRE strain related to the VRE strain of the associated index patients.

In only 3 of 19 cases was VRE isolated from > 1 blood culture and accompanied by signs and symptoms of infection, making the bacteremia clinically significant. Interestingly, the researchers note, the 3 patients with clinically significant bacteremia had no positive contacts. The other 16 cases could possibly be due to the many lines, devices, and other sources of potential contamination, the researchers say.

And it took time to transmit the pathogens—72 hours for positive contacts (standard deviation ± 67.9). Because extended contact time was needed, the researchers question the effectiveness of isolation in single or cohort rooms and other barrier precautions except for those who are part of vulnerable groups, such as transplant or cancer patients. They say hand hygiene is probably a better method of control, and isolation makes only "a minor contribution."

Source: Mutters NT, Brooke RJ, Frank U, Heeg K. *Am J Infect Control.* 2013;41(9):778-781.
doi: 10.1016/j.ajic.2012.11.019.

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