Drug Monitor

Antidepressant Use: No Increased Risk of Myocardial Infarction (MI)

Selective serotonin reuptake inhibitor (SSRI) antidepressants have been considered a better option for many patients because they aren't associated with the cardiovascular risks of tricyclic antidepressants. However, is that the case for the newer serotonin-norepinephrine reuptake inhibitors? Researchers from St. Louis VA Medical Center (VAMC), Washington University, and Saint Louis University, all in St. Louis, Missouri; and Central Arkansas Veterans Heathcare System in North Little Rock, analyzed the records of 93,653 VA patients, aged 25 to 80 years, to see whether these antidepressants raise or lower the risk of MI and all-cause mortality.

VA guidelines mandate 12 weeks of antidepressants for a patient experiencing a new episode of depression. Of depressed patients in the study, 79% received guideline-concordant care, 8% received no antidepressants, and 13% received 1 to 11 weeks of antidepressant treatment. Patients were considered treated with antidepressants if they received 12 or more continuous weeks of treatment with the same drug and had refilled the prescription at least once. A patient was considered not treated if they received less than 12 weeks of any drug. SSRIs were the most common antidepressants received for 12 weeks or longer.

Medication was not only associated with a lower risk of MI, but also appeared to alleviate the higher risk of MI attributable to depression. Receiving an antidepressant for 12 or more weeks was associated with significantly reduced rates of incident MI across classes of antidepressants, compared with receiving less than 12 weeks' treatment. Risk of all-cause mortality also was reduced with 12 weeks' treatment with all classes of antidepressants.

Why the treatment reduced the risk of MI and mortality isn't certain, the researchers say. They suggest it might be due to reducing depression through pharmacotherapy, to a direct effect of the drugs themselves, or to the fact that patients who use 12 or more weeks of antidepressants are also more likely to comply with other prescriptive health behaviors.

The researchers also computed post hoc analyses to determine if a dose-response effect existed for long-term use. Their results indicate an average of a 3% reduction in risk for every additional month of antidepressant therapy across drug class.

Source: Am J Med. 2011;124(4):318-324. doi:10.1016/j.amjmed.2010.11.015

Propofol and Intensive Care Unit (ICU) Infections

While generally safe, propofol has nonetheless been associated with postoperative and nosocomial infections. Possible contamination of the drug has been identified as a cause for some, but can't answer for all. Researchers from King Abdulaziz Medical City and King Saud Bin Abdulaziz University of Health Sciences, both in Riyadh, Saudi Arabia, conducted a post hoc nested cohort study within a randomized controlled trial to find out the role preservative-free propofol infusion might independently play in adverse outcomes.

They compared 2 groups of patients: 399 patients who did not receive propofol and 124 who did. The researchers calculated the cumulative and average daily dose of propofol for the first 7 ICU days. Patients were stratified according to the cumulative dose (group I, cumulative dose $\leq$ 357 mg; group II, cumulative dose $>$ 357 mg). The researchers also calculated average daily caloric intake, average blood glucose level (the larger study compared intensive insulin therapy with conventional insulin therapy), and average daily doses of insulin. The endpoints of the study were ICU-acquired infections; ICU-acquired sepsis; ICU and hospital length of stay; and ICU and hospital mortality.

The propofol group had a higher rate of ICU-acquired infection (50% vs 35%), but also a trend toward lower ICU mortality (11% vs 17%) and significantly lower hospital mortality (18% vs 33%). There were no significant differences between the 2 groups in ICU or hospital length of stay.

In adjusted analyses, the use of propofol was associated with a nearly double risk of ICU-acquired infection, ICU-acquired sepsis, and septic shock. Patients who received more than the median propofol dose ($>$ 357 mg) had a higher rate of infections, and a trend toward higher rates of severe sepsis and septic shock.

The researchers suggest a number of potential mechanisms through which propofol might increase the risk of infection in ICU patients. One is that propofol impairs monocyte and neutrophil function, and reduces bacterial clearance. The researchers also note that the higher caloric intake from propofol could influence the outcome, since moderate caloric intake is associated with better outcomes. And finally, extrinsic contamination is possible, though the risk

of nosocomial infection secondary to contamination has been reported to be extremely low in ICU patients.

Another possibility is that lipid-based medications like propofol support rapid growth of microorganisms. A modified formula containing ethylenediaminetetraacetic acid (EDTA), a preservative that inhibits the growth of microorganisms, has been introduced in the United States; there have been no further cluster outbreaks of postoperative nosocomial infections with propofol infusions, the researchers say. However, they add, EDTA-containing formulations of propofol are not considered an antimicrobially preserved product under U.S. pharmacopeia standards.

If the infection is driven by caloric intake, a new lipid-free prodrug propofol may help. Fospropofol disodium is not only lipid-free, but water soluble, which is expected to lower the risk of infection. It recently has been approved by the FDA for monitored sedation in adults undergoing diagnostic or therapeutic procedures.

The researchers conclude with the recommendation that, until further studies validate their findings, it might be wise to avoid prolonged use of propofol, especially preservative-free formulations, for continuous sedation of critically ill patients.

Source: Am J Infect Control. 2011;39(3):141-147. doi:10.1016/j.ajic.2010.05.027

Long-Term Treatment Raises Rhinosinusitis Cure Rates

Chronic rhinosinusitis (CRS) with nasal polyposis is a heavy-duty form of rhinosinusitis, causing nasal blockage, facial pain, and hyposmia. Patients experiencing the condition are prone to relapse, and response to therapy is frequently incomplete. Researchers from Ninewells Hospital and University of Dundee, both in the United Kingdom, suggest that starting off with 2 weeks of oral steroids, followed by 26 weeks of topical steroids, is an effective way to knock the infection out.

In their study, 60 nonsmoking adults with CRS and moderate-sized or larger nasal polyps were randomly assigned to receive oral prednisolone 25 mg/day or placebo for 2 weeks, followed by (in both groups) 2 doses daily of fluticasone propionate nasal drops 400 µg bid for 8 weeks, then 2 doses daily of fluticasone propionate nasal spray 200 µg bid for 18 weeks. From the first screening until the end of the study, patients were forbidden to ingest any other rhinitis medications.

The primary outcomes measures were polyp grading, hyposmia score, quality of life (QOL), symptoms, nasal patency, adrenal function, and bone turnover. Patients in either treatment group who had an improvement of more than 1 minimal important difference in either polyp grading or hyposmia visual analogue scale by the end of 6 months were classified as responders. Fifty-one patients completed the study.

The mean decrease in polyp grade from baseline to 2 weeks was 2.1 units in the prednisolone group and 0.1 in the placebo group, for a mean difference of –1.8 units between the groups. The difference was –1.08 units at 10 weeks, and –0.8 unit at 28 weeks.

The hyposmia score from baseline to 2 weeks showed a decrease of 31.12 mm in the prednisolone group and 1.41 mm in the placebo group, a –28.33 mm mean difference. At 28 weeks, the mean difference was –12.13 mm.

Most (83%) of the 25 patients in the prednisolone group improved by more than the minimal important difference in either polyp grade or hyposmia visual analogue scale (VAS) by 28 weeks, compared with 17 (57%) in the placebo group. Similar number of patients in both groups reported adverse events (19 in the prednisolone group, vs 18 in the placebo group). No adverse events were defined as serious. Notably, the researchers found no residual adrenal suppression or reduction in osteoblast activity at 10 or 28 weeks.

Nasal obstruction and impaired sense of smell, the 2 main symptoms of CRS with nasal polyposis, are also 2 of the main reasons CRS affects QOL. The researchers say although evidence indicates that oral steroids have a direct stimulatory effect on olfactory neurons, the sustained improvement in olfaction they observed in their study suggests a reduction in local mucosal inflammation and edema as the mechanism. They also found reductions in systemic markers of eosinophil activation and inflammation with systemic, but not topic, corticosteroid therapy, further supporting their hypothesis, they say, that the reduction in polyp size and improved sense of smell were due to local anti-inflammatory effects rather than systemic steroid spillover.

The researchers say that, to their knowledge, no previous randomized controlled trial has evaluated the long-term effects of oral steroid therapy for CRS with nasal polyposis.

Source: Ann Intern Med. 2011;154(5):293-302.