Tips from Other Journals

Tips from Other Journals are written by the medical editors of *American Family Physician.*

The trade names of drugs listed in Tips from Other Journals are based on what is currently available and not necessarily the brand of drug that was used in the study being discussed.

Bipolar Disorder I in Children: Which Treatment Works Best?

Background: Although antipsychotic medications are often prescribed for childhood mania, few trials have examined their benefits and adverse effects in this population. Several randomized trials have reported that atypical antipsychotics are helpful for treating mania in adolescents, but these trials have not included children younger than 10 years or compared the relative benefits of different medications. Geller and colleagues conducted a randomized controlled trial to determine the most effective medication for treating mania in children and adolescents.

The Study: In the Treatment of Early Age Mania study, outpatients six to 15 years of age were randomized to receive lithium, divalproex (Depakote), or risperidone (Risperdal). Eligible participants had a *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV) diagnosis of bipolar I disorder (manic or mixed episode) for at least four consecutive weeks at study enrollment, with a Children's Global Assessment Scale (CGAS) score of 60 or less. Persons with coexisting attention-deficit/hyperactivity, oppositional defiant, or conduct disorder were allowed to participate because these are common comorbidities in childhood mania. Those with a history of schizophrenia, pervasive developmental disorder, major medical or neurologic disease, substance abuse, or any previous psychotropic drug use (including atypical antipsychotics, lithium, and anticonvulsants) were excluded. Concurrent use of most psychiatric medications was not permitted during the study, except for maintenance doses of methylphenidate (Ritalin) and amphetamine preparations.

Participants were started at low doses of their study medication, with titration upward if there was minimal or no improvement based on weekly assessments using the Clinical Global Impressions for Bipolar Illness Improvement–Mania (CGI-BP-IM) scores. Up to 10 tablets of chlorpromazine (25 mg) were allowed as a rescue medication during the first four weeks. The primary outcome measure was improvement in the CGI-BP-IM score over an eight-week period.

Results: The study analyzed 89 persons who received risperidone, 90 who received lithium, and 100 who received divalproex. There was no significant difference between groups regarding medication adherence rates, stimulant medication use, the need for rescue medication, or discontinuance rates from adverse events. Overall, those treated with risperidone had a significantly higher response rate (68.5 percent) than those treated with lithium (35.6 percent) or divalproex (24.0 percent). There was no significant difference in response rates between lithium and divalproex. Similar response rates were found during subgroup analysis based on age (six to 12 years versus 13 to 15 years), associated psychosis, and the presence or absence of concurrent stimulant use. The risperidone group also had significantly greater improvement in CGAS scores and absence of mania by DSM-IV criteria at the end of the study, compared with the lithium and divalproex groups. No serious medication-related adverse events were identified, although participants in the risperidone group did have significantly greater weight gain than those in the other groups.

Conclusion: Risperidone is significantly more effective than lithium or divalproex ▶

in the initial management of mania in children. However, it is also associated with greater weight gain, which may raise concerns about its use for long-term management in children.

KENNETH T. MOON, MD

Source: Geller B, et al. A randomized controlled trial of risperidone, lithium, or divalproex sodium for initial treatment of bipolar I disorder, manic or mixed phase, in children and adolescents. *Arch Gen Psychiatry.* May 2012; 69(5):515-528.

Prolonged Clopidogrel Use After Cardiac Stenting Is Not Beneficial

Background: American and European cardiology societies recommend six to 12 months of dual-antiplatelet therapy with aspirin and clopidogrel (Plavix) after drug-eluting stent placement to prevent late stent thrombosis. The data used to support these guidelines, however, are derived from older observational studies that included only patients who received clopidogrel before stenting. Because the optimal duration and risk-benefit ratio of dual-antiplatelet therapy are not known, Valgimigli and colleagues compared outcomes with six and 24 months of dual-antiplatelet therapy in patients receiving drug-eluting or bare-metal stents.

The Study: The Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study was a multicenter, prospective, open-label trial in which patients were randomly assigned to a bare-metal stent or one of three U.S. Food and Drug Administration–approved drug-eluting stents. Patients were screened for inclusion between 2006 and 2008. Those 18 years and older with chronic stable coronary artery disease or acute coronary syndromes were eligible for inclusion if they had at least one vessel appropriate for stenting. Inclusion criteria were broad to reflect clinical practice, and exclusions were limited to allergy to aspirin or clopidogrel, planned surgery within 24 months of stenting, need for oral anticoagulation, history of bleeding diathesis, active bleeding in the preceding six months, pregnancy, or life expectancy of less than 24 months.

All patients received loading doses of aspirin and clopidogrel, then 80 to 160 mg of aspirin and 75 mg of clopidogrel daily. After 30 days, patients were randomized to receive six or 24 months of aspirin and clopidogrel. Participants followed up for study visits after 30 days, then every six months for up to two years for clinical examination, electrocardiography, and adherence monitoring. Additionally, nurses contacted participants monthly. The primary end point was death from any cause, nonfatal myocardial infarction, or cerebrovascular accident. The key safety end point was bleeding rates using Thrombolysis In Myocardial Infarction criteria and the BleedScore.

Results: Of the 2,013 patients recruited, 1,970 patients were randomized to six or 24 months of treatment. The two groups had similar baseline characteristics and included similar numbers of each stent type. The median age was 69 years; approximately 25 percent of patients had diabetes mellitus or previous myocardial infarction, and two-thirds of patients presented with acute coronary syndrome. There was no difference between the groups in all-cause mortality, cardiovascular death, nonfatal myocardial infarction or stroke, or stent thrombosis. At two years, the event rate for the primary end point was 10.1 percent for the 24-month treatment group and 10.0 percent in the six-month treatment group. However, there was an approximately twofold increase in bleeding complications requiring medical or surgical treatment or transfusion in the 24-month treatment group.

Conclusion: Extending clopidogrel therapy beyond six months after stent placement does not reduce death or ischemic events, and increases the risk of bleeding complications.

AMY CRAWFORD-FAUCHER, MD

Source: Valgimigli M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation.* April 24, 2012;125(16):2015-2026.

Preventing Post-ERCP Pancreatitis with Indomethacin

Background: The most common serious complication of endoscopic retrograde cholangiopancreatography (ERCP) is acute pancreatitis. Currently, temporary pancreatic ▶

stenting is the only intervention proven to reduce the risk of post-ERCP pancreatitis. Nonsteroidal anti-inflammatory drugs (NSAIDs), administered as a single rectal dose, have shown preliminary promise in a meta-analysis, although no definitive evidence is available. Elmunzer and colleagues conducted a multicenter, randomized controlled trial of rectal indomethacin (Indocin) for preventing post-ERCP pancreatitis in high-risk patients.

The Study: Patients were randomized to receive two 50-mg indomethacin suppositories or placebo immediately after undergoing ERCP. Patients were then observed in the recovery area for at least 90 minutes, and were followed for 30 days to monitor for post-procedure events and complications. Patients were eligible if they met at least one of the major criteria for post-ERCP pancreatitis: previous post-ERCP pancreatitis, pancreatic or precut sphincterotomy, clinical suspicion of sphincter of Oddi dysfunction, pneumatic dilatation of an intact biliary sphincter, ampullectomy, or more than eight cannulation attempts. Eligibility also could be met with two or more minor criteria: women younger than 50 years, history of recurrent pancreatitis, multiple contrast injections into the pancreatic duct with at least one injection to the pancreatic tail, opacification of pancreatic acini caused by excessive contrast injection, or the brush acquisition of a pancreatic duct cytologic specimen. Patients were excluded if they had active pancreatitis or peptic ulcer disease, were already using NSAIDs, or had a serum creatinine level greater than 1.4 mg per dL (123.76 μmol per L). The primary outcome was the development of post-ERCP pancreatitis.

Results: Investigators enrolled 602 patients (295 were randomized to receive indomethacin and 307 to receive placebo), of whom most (82.3 percent) were suspected to have sphincter of Oddi dysfunction. Post-ERCP pancreatitis developed in 79 patients overall, with significantly fewer episodes occurring in the indomethacin group compared with the placebo group (9.2 versus 16.9 percent; $P = .005$; absolute risk reduction = 7.7 percentage points; relative risk reduction = 46 percent). The number needed to treat to prevent one episode of post-ERCP pancreatitis was 13. Secondary outcome analysis found that patients in the indomethacin group were less likely to experience moderate or severe post-ERCP pancreatitis (4.4 versus 8.8 percent; $P = .03$), and had a shorter median length of hospital stay (3.5 versus 4.0 days; $P < .001$). Adverse events, such as clinically significant bleeding, were similar between groups. No myocardial infarctions, strokes, or deaths were reported at the 30-day follow-up.

Conclusion: Compared with placebo, a single dose of rectal indomethacin significantly reduced the likelihood of post-ERCP pancreatitis, the likelihood of moderate or severe pancreatitis, and the length of hospital stay in patients at high risk of this complication.

KENNETH T. MOON, MD

Source: Elmunzer BJ, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med.* April 12, 2012;366(15):1414-1422. ■