Multiple genetic loci for bone mineral density and fractures.

Methylnaltrexone for opioid-induced constipation in advanced illness.
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SPECIAL ARTICLE
The collective dynamics of smoking in a large social network.
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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL
Case 16-2008: a 46-year-old woman with bone pain.

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Cricothyroidotomy.
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**PERSPECTIVES**


On November 22, 2007, viewers of the nationally televised Thanksgiving Day football game between the Dallas Cowboys and the New York Jets witnessed the launch of the first direct-to-consumer advertising (DTCA) campaign for percutaneous transluminal coronary angioplasty (PTCA) with a drug-eluting coronary stent. The airing of “Life Wide Open,” the 60-second commercial for Cypher, the sirolimus-coated stent produced by the Cordis division of Johnson & Johnson, marked the dawn of a new era in medical DTCA, which has for the past decade focused on brand-name pharmaceutical agents. To many consumers, the stent ad may no


In November 1996, the Wall Street Journal reported that Eli Lilly was paying homeless alcoholics from a local shelter to participate in safety testing of new drugs at its trial site in Indianapolis. “These individuals want to help society,” asserted Lilly’s director of clinical pharmacology. The subjects, however, said they took part for easy money and free room and board. Although Lilly reportedly offered the lowest per diem in the business, it managed to attract poor subjects from all over the country. The medical director of the local Homeless Initiative Program said Lilly had created a “shadow economy” of paid education.


I came home the other night clutching a scrap of paper towel with a mother’s cell-phone number scribbled on it. I had been precepting in the residents’ pediatric primary care clinic, and an intern had presented a patient: a 20-month-old boy who had been brought in by his mother because he was vomiting. He’d thrown up seven times since 2 that morning. No diarrhea, but he wasn’t eating or drinking much. Still, he didn’t look dehydrated, his mother said he’d had several wet diapers, and when the intern examined him, she found his diaper wet again. The intern said he...

**ARTICLES**


Early-onset, severe retinal dystrophy caused by mutations in the gene encoding retinal pigment epithelium-specific 65-kD protein (RPE65) is associated with poor vision at birth and complete loss of vision in early adulthood. We administered to three young adult patients subretinal injections of recombinant adeno-associated virus vector 2/2 expressing RPE65 complementary DNA (cDNA) under the control of a human RPE65 promoter. There were no serious adverse events. There was no clinically significant change in visual acuity or in peripheral visual fields on Goldmann perimetry in any of the three patients. We detected no change in retinal responses on electroretinography. One patient had significant improvement in visual function on microperimetry and on dark-adapted perimetry. This patient also showed improvement in a subjective test of visual mobility. These findings provide support for further clinical studies of this experimental approach in other patients with mutant RPE65.


In this 12-week trial, we aimed to determine the efficacy of prucalopride, a selective, high-affinity 5-hydroxytryptamine4 receptor agonist, in patients with severe chronic constipation. In our multicenter, randomized, placebo-controlled, parallel-group, phase 3 trial, patients (cDNA) under the control of a human RPE65 promoter. There were no serious adverse events. There was no clinically significant change in visual acuity or in peripheral visual fields on Goldmann perimetry in any of the three patients. We detected no change in retinal responses on electroretinography. One patient had significant improvement in visual function on microperimetry and on dark-adapted perimetry. This patient also showed improvement in a subjective test of visual mobility. These findings provide support for further clinical studies of this experimental approach in other patients with mutant RPE65.

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and 46.6% of those receiving 4 mg of prucalopride had an increase in the number of spontaneous, complete bowel movements of one or more per week, on average, as compared with 25.8% in the placebo group (P<0.001 for both comparisons). All other secondary efficacy end points, including patients’ satisfaction with their bowel function and treatment and their perception of the severity of their constipation symptoms, were significantly improved with the use of 2 or 4 mg of prucalopride as compared with placebo, at week 12. The most frequent treatment-related adverse events were headache and abdominal pain. There were no significant cardiovascular effects of treatment. Over 12 weeks, prucalopride significantly improved bowel function and reduced the severity of symptoms in patients with severe chronic constipation. Larger and longer trials are required to further assess the risks and benefits of the use of prucalopride for chronic constipation.


Antifibrinolytic agents are commonly used during cardiac surgery to minimize bleeding and to reduce exposure to blood products. We sought to determine whether aprotinin was superior to either tranexamic acid or aminocaproic acid in decreasing massive postoperative bleeding and other clinically important consequences. In this multicenter, blinded trial, we randomly assigned 2331 high-risk cardiac surgical patients to one of three groups: 781 received aprotinin, 770 received tranexamic acid, and 780 received aminocaproic acid. The primary outcome was massive postoperative bleeding. Secondary outcomes included death from any cause at 30 days. The trial was terminated early because of a higher rate of death in patients receiving aprotinin. A total of 74 patients (9.5%) in the aprotinin group had massive bleeding, as compared with 93 (12.1%) in the tranexamic acid group and 94 (12.1%) in the aminocaproic acid group (relative risk in the aprotinin group for both comparisons, 0.79; 95% confidence interval [CI], 0.59 to 1.05). At 30 days, the rate of death from any cause was 6.0% in the aprotinin group, as compared with 3.9% in the tranexamic acid group (relative risk, 1.55; 95% CI, 0.99 to 2.42) and 4.0% in the aminocaproic acid group (relative risk, 1.52; 95% CI, 0.98 to 2.36). The relative risk of death in the aprotinin group, as compared with that in both groups receiving lysine analogues, was 1.53 (95% CI, 1.06 to 2.22). Despite the possibility of a modest reduction in the risk of massive bleeding, the strong and consistent negative mortality trend associated with aprotinin, as compared with the lysine analogues, precludes its use in high-risk cardiac surgery.


Leber’s congenital amaurosis (LCA) is a group of inherited blinding diseases with onset during childhood. One form of the disease, LCA2, is caused by mutations in the retinal pigment epithelium–specific 65-kDa protein gene (RPE65). We investigated the safety of subretinal delivery of a recombinant adeno-associated virus (AAV) carrying RPE65 complementary DNA (cDNA) (ClinicalTrials.gov number, NCT00516477 [ClinicalTrials.gov]). Three patients with LCA2 had an acceptable local and systemic adverse-event profile after delivery of AAV2.hRPE65v2. Each patient had a modest improvement in measures of retinal function on subjective tests of visual acuity. In one patient, an asymptomatic macular hole developed, and although the occurrence was considered to be an adverse event, the patient had some return of retinal function. Although the follow-up was very short and normal vision was not achieved, this study provides the basis for further gene therapy studies in patients with LCA.


We hypothesized that percutaneous coronary intervention (PCI) preceded by early treatment with abciximab plus half-dose reteplase (combination-facilitated PCI) or with abciximab alone (abciximab-facilitated PCI) would improve outcomes in patients with acute ST-segment elevation myocardial infarction, as compared with abciximab administered immediately before the
procedure (primary PCI). In this international, double-blind, placebo-controlled study, we randomly assigned patients with ST-segment elevation myocardial infarction who presented 6 hours or less after the onset of symptoms to receive combination-facilitated PCI, abciximab-facilitated PCI, or primary PCI. All patients received unfractionated heparin or enoxaparin before PCI and a 12-hour infusion of abciximab after PCI. The primary end point was the composite of death from all causes, ventricular fibrillation occurring more than 48 hours after randomization, cardiogenic shock, and congestive heart failure during the first 90 days after randomization. A total of 2452 patients were randomly assigned to a treatment group. Significantly more patients had early ST-segment resolution with combination-facilitated PCI (43.9%) than with abciximab-facilitated PCI (33.1%) or primary PCI (31.0%; P=0.01 and P=0.003, respectively). The primary end point occurred in 9.8%, 10.5%, and 10.7% of the patients in the combination-facilitated PCI group, abciximab-facilitated PCI group, and primary-PCI group, respectively (P=0.55); 90-day mortality rates were 5.2%, 5.5%, and 4.5%, respectively (P=0.49). Neither facilitation of PCI with reteplase plus abciximab nor facilitation with abciximab alone significantly improved the clinical outcomes, as compared with abciximab given at the time of PCI, in patients with ST-segment elevation myocardial infarction.


Treatment with the direct thrombin inhibitor bivalirudin, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, results in similar suppression of ischemia while reducing hemorrhagic complications in patients with stable angina and non-ST-segment elevation acute coronary syndromes who are undergoing percutaneous coronary intervention (PCI). The safety and efficacy of bivalirudin in high-risk patients are unknown. We randomly assigned 3602 patients with ST-segment elevation myocardial infarction who presented within 12 hours after the onset of symptoms and who were undergoing primary PCI to treatment with heparin plus a glycoprotein IIb/IIIa inhibitor or to treatment with bivalirudin alone. The two primary end points of the study were major bleeding and combined adverse clinical events, defined as the combination of major bleeding or major adverse cardiovascular events, including death, reinfarction, target-vessel revascularization for ischemia, and stroke (hereinafter referred to as net adverse clinical events) within 30 days. Anticoagulation with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, resulted in a reduced 30-day rate of net adverse clinical events (9.2% vs. 12.1%; relative risk, 0.76; 95% confidence interval [CI] 0.63 to 0.92; P=0.005), owing to a lower rate of major bleeding (4.9% vs. 8.3%; relative risk, 0.60; 95% CI, 0.46 to 0.77; P<0.001). There was an increased risk of acute stent thrombosis within 24 hours in the bivalirudin group, but no significant increase was present by 30 days. Treatment with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, resulted in significantly lower 30-day rates of death from cardiac causes (1.8% vs. 2.9%; relative risk, 0.62; 95% CI, 0.40 to 0.95; P=0.03) and death from all causes (2.1% vs. 3.1%; relative risk, 0.66; 95% CI, 0.44 to 1.00; P=0.047). In patients with ST-segment elevation myocardial infarction who are undergoing primary PCI, anticoagulation with bivalirudin alone, as compared with heparin plus glycoprotein IIb/IIIa inhibitors, results in significantly reduced 30-day rates of major bleeding and net adverse clinical events.


Bone mineral density influences the risk of osteoporosis later in life and is useful in the evaluation of the risk of fracture. We aimed to identify sequence variants associated with bone mineral density and fracture. We performed a quantitative trait analysis of data from 5861 Icelandic subjects (the discovery set), testing for an association between 301,019 single-nucleotide polymorphisms (SNPs) and bone mineral density of the hip and lumbar spine. We then tested for an association between 74 SNPs (most of which were implicated in the discovery set) at 32 loci in replication sets of Icelandic, Danish, and Australian subjects (4165, 2269, and 1491 subjects, respectively). Sequence variants in five genomic regions were significantly associated with bone mineral density in the discovery set and were confirmed in the replication sets (combined P values, 1.2x10⁻⁷ to 2.0x10⁻²¹). Three regions are close to or within genes previously shown to be important to the biologic characteristics of bone: the reccip ligand gene (RANKL) (chromosomal location, 13q14), the osteoprotegerin gene (OPG) (8q24), and the estrogen receptor 1 gene (ESR1) (6q25). The two other regions are close to the zinc finger and BTB domain containing 40 gene (ZBTB40) (1p36) and the major histocompatibility complex region (6p21). The 1p36, 8q24, and 6p21 loci were also associated with osteoporotic fractures, as were loci at 18q21, close to the receptor acti gene (RANK), and loci at 2p16 and 11p11. We have dis-
covered common sequence variants that are consistently associated with bone mineral density and with low-trauma fractures in three populations of European descent. Although these variants alone are not clinically useful in the prediction of risk to the individual person, they provide insight into the biochemical pathways underlying osteoporosis.


Constipation is a distressing side effect of opioid treatment. As a quaternary amine, methylnaltrexone, a µ-opioid-receptor antagonist, has restricted ability to cross the blood–brain barrier. We investigated the safety and efficacy of subcutaneous methylnaltrexone for treating opioid-induced constipation in patients with advanced illness. A total of 133 patients who had received opioids for 2 or more weeks and who had received stable doses of opioids and laxatives for 3 or more days without relief of opioid-induced constipation were randomly assigned to receive subcutaneous methylnaltrexone (at a dose of 0.15 mg per kilogram of body weight) or placebo every other day for 2 weeks. Coprimary outcomes were laxation (defecation) within 4 hours after the first dose of the study drug and laxation within 4 hours after two or more of the first four doses. Patients who completed this phase were eligible to enter a 3-month, open-label extension trial. In the methylnaltrexone group, 48% of patients had laxation within 4 hours after the first study dose, as compared with 15% in the placebo group, and 52% had laxation without the use of a rescue laxative within 4 hours after two or more of the first four doses, as compared with 8% in the placebo group (P<0.001 for both comparisons). The response rate remained consistent throughout the extension trial. The median time to laxation was significantly shorter in the methylnaltrexone group than in the placebo group. Evidence of withdrawal mediated by central nervous system opioid receptors or changes in pain scores was not observed. Abdominal pain and flatulence were the most common adverse events. Subcutaneous methylnaltrexone rapidly induced laxation in patients with advanced illness and opioid-induced constipation. Treatment did not appear to affect central analgesia or precipitate opioid withdrawal.

SPECIAL ARTICLE


The prevalence of smoking has decreased substantially in the United States over the past 30 years. We examined the extent of the person-to-person spread of smoking behavior and the extent to which groups of widely connected people quit together. We studied a densely interconnected social network of 12,067 people assessed repeatedly from 1971 to 2003 as part of the Framingham Heart Study. We used network analytic methods and longitudinal statistical models. Discrimible clusters of smokers and nonsmokers were present in the network, and the clusters extended to three degrees of separation. Despite the decrease in smoking in the overall population, the size of the clusters of smokers remained the same across time, suggesting that whole groups of people were quitting in concert. Smokers were also progressively found in the periphery of the social network. Smoking cessation by a spouse decreased a person’s chances of smoking by 67% (95% confidence interval [CI], 59 to 73). Smoking cessation by a sibling decreased the chances by 25% (95% CI, 14 to 35). Smoking cessation by a friend decreased the chances by 36% (95% CI, 12 to 55). Among persons working in small firms, smoking cessation by a coworker decreased the chances by 34% (95% CI, 5 to 56). Friends with more education influenced one another more than those with less education. These effects were not seen among neighbors in the immediate geographic area. Network phenomena appear to be relevant to smoking cessation. Smoking behavior spreads through close and distant social ties, groups of interconnected people stop smoking in concert, and smokers are increasingly marginalized socially. These findings have implications for clinical and public health interventions to reduce and prevent smoking.

CLINICAL THERAPEUTICS


This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author’s clinical recommendations. A busy 28-year-old professional consults his physician for advice on long-standing hay fever. He reports having itchy eyes and an itchy nose, lacrimation, sneezing, rhinorrhea, and nasal congestion during the summer months. In previous years, he tried various antihistamines...
IMAGES IN CLINICAL MEDICINE


An 86-year-old woman with severe symptomatic aortic stenosis was referred for routine preoperative cardiac catheterization. During the procedure, pronounced tortuosity of the catheter was noted. Subsequent administration of intravenous contrast material revealed the presence of a markedly tortuous thoracic and abdominal aorta with no evidence of a localized aneurysm (Panel A) and with a clearly visible Judkins catheter (arrow) and venous catheter (arrowhead). The peripheral circulation was normal in both upper and lower limbs at physical examination, and the kidney function was not compromised. Chest radiography showed multiple vertebral compression fractures and pronounced kyphosis (Panel B). Two photographs of the . . .


A 46-year-old man with a history of cerebral palsy presented with difficulty in breathing, which had gradually increased during the previous 2 weeks. He was admitted to the intensive care unit with a diagnosis of sepsis, for which he received intravenous fluids, antibiotics, and mechanical ventilation. Computed tomography of the abdomen showed a severely distended colon with fecal stasis compressing the abdominal organs and the diaphragm. There were no signs of colonic perforation. After initial conservative measures were unsuccessful in evacuating the impaction, multiple enemas with the use of sodium phosphate and soapsuds finally dislodged the blockage after 2 . . .


A 67-year-old woman presented with dyspnea and peripheral edema due to severe tricuspid regurgitation. Having had rheumatic heart disease, she had undergone replacement of the mitral and aortic valves with Starr–Edwards heart valves 38 years earlier. During her recent admission, echocardiography showed a transaortic valve gradient of 18 mm Hg, a transmitral valve gradient of 4 mm Hg, and elevated systolic pressure, at 70 mm Hg, in the pulmonary artery. She underwent a preoperative right and left heart catheterization for tricuspid-valve replacement; both mechanical mitral and aortic valves were functioning normally (Panel A, systolic phase, aortic valve open, arrow; Panel . . .


A 14-year-old girl presented with a traumatic injury to the right eye from a water-bottle cap, caused by the increasingly popular adolescent activity of twisting and crushing an empty plastic water bottle, with the cap loosened, until the cap flies off because of increased pressure. The patient’s vision was limited to hand motions, and the intraocular pressure was 13 mm Hg. A 70% hyphema was present. Vision improved slowly with clearing of the hyphema. On day 4, she experienced severe eye pain and decreased vision. The blood clot in the anterior chamber (white arrow) had decreased in size, and a . . .

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL


A 46-year-old woman was seen in the orthopedic oncology clinic of this hospital because of pain in the right hip and leg. Several months earlier, pain had developed in her right upper medial thigh and had gradually increased in intensity despite treatment with ibuprofen, pantoprazole, and acetaminophen–codeine. Four weeks before this evaluation, she was seen at another facility. On examination, her vital signs were normal; her height was 156.2 cm, and her weight 44.5 kg. There was tenderness over the right medial adductor magnus muscle, full range of motion of the hip joint, and pain on standing. Two weeks later, . . .


A 63-year-old man was admitted to this hospital because of a mass in the left kidney and pulmonary nodules. The patient had been well until approximately 5 months before admission, when mild nausea, loss of appetite, abdominal pain, and constipation developed, followed by fatigue, weight loss of 3.2 kg, and a nonproductive cough. One month before admission, he saw his primary care physician. Examination revealed scrotal varicoceles that were new and varicosities of both legs that were unchanged from previous examinations; results of the remainder of the examination were normal. Laboratory-test results and radiographs of the upper gastrointestinal tract that . . .
CLINICAL PRACTICE


This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors’ clinical recommendations.

The parents of a 6-year-old girl bring her to a pediatrician because of breast development. Her medical history is unremarkable. The parents are of average height, and the mother reports first menstruating when she was 11 years old. At physical examination, the girl is 125 cm tall (in the 97th percentile for her age), weighs 28 kg, and has a body-mass index . . .

REVIEW ARTICLE


The hepatopulmonary syndrome is characterized by a defect in arterial oxygenation induced by pulmonary vascular dilatation in the setting of liver disease; patients of all ages can be affected. This clinical syndrome has three components: liver disease, pulmonary vascular dilatation, and a defect in oxygenation. A classification of the severity of the hepatopulmonary syndrome based on abnormalities in oxygenation is vital because severity influences survival and is useful in determining the timing and risks of liver transplantation (Table 1). The vascular component includes diffuse or localized dilated pulmonary capillaries and, less commonly, pleural and pulmonary arteriovenous communications. . . .

VIDEOS IN CLINICAL MEDICINE


Indications Cricothyroidotomy is an emergent procedure performed on patients experiencing severe respiratory distress in whom orotracheal or nasotracheal intubation has failed. The procedure involves making an incision in the cricothyroid membrane, which lies between the thyroid and cricoid cartilages, followed by inserting a tracheostomy tube, which allows ventilation. This video describes how to perform a cricothyroidotomy in an adult. The major indication for cricothyroidotomy is the inability to establish an airway by orotracheal or nasotracheal intubation. Failure to secure an orotracheal or nasotracheal airway may be due to factors such as difficult patient anatomy; excessive blood in the mouth or . . . .