

Long-acting injectable naltrexone reduces heavy drinking

Clinical question Is a long-acting injectable formulation of naltrexone effective in the management of alcohol dependence?

Bottom line Long-acting injectable naltrexone reduces heavy drinking days in the treatment of alcohol dependence but does not increase total abstinence rates. (Level of evidence = 1b)

Garbutt JC, Kranzler HR, O'Malley SS, et al, for the Vivitrex Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence. A randomized controlled trial. *JAMA*. 2005;293:1617-1625.

Synopsis Oral naltrexone is effective for treatment of alcohol dependence, but patient compliance with a daily medication regimen is poor. To evaluate the efficacy of a long-acting injectable formulation of naltrexone (Vivitrex), the investigators identified 627 patients, 18 years or older, meeting the DSM-IV criteria for alcohol dependence. Study subjects were randomized in a double-blind fashion (allocation concealment uncertain) to receive a monthly intramuscular injection of naltrexone, 190 mg or 380 mg, or matched placebo. All patients also received 12 sessions of low-intensity psychosocial intervention designed to facilitate direct feedback of addiction-related consequences. Outcomes were assessed by individuals blinded to treatment group assignment. Follow-up for 6 months was complete for 87% of the subjects. Using intention-to-treat analysis, the 380-mg dose of long-acting naltrexone resulted in a statistically significant reduction in heavy drinking days compared with placebo (hazard ratio = 0.75; 95% CI, 0.60-0.94; number needed to treat [NNT] = 20; 12 - 88). There was no significant difference in heavy drinking days between the 190-mg naltrexone group and placebo. The number of patients maintaining complete abstinence during the trial (6%) was similar among the 3 groups. Patients maintaining abstinence for at least 1 week before study initiation responded more favorably to treatment than those who were actively drinking. Study discontinuation because of adverse events (nausea, headache, and fatigue) was significantly higher in the 380-mg naltrexone group than in the placebo group (14.1% versus 6.7%; number needed to treat to harm = 14).

Intermittent = continuous therapy for mild persistent asthma

Clinical question Does continuous therapy with anti-inflammatory drugs improve outcomes for patients with mild persistent asthma?

Bottom line Intermittent therapy, as measured by the outcomes that matter, is as effective as continuous therapy with oral zafirlukast or inhaled budesonide for patients with very mild but persistent asthma. Note that patients had a clear plan of action for when symptoms flared up: Begin inhaled budesonide in the "yellow zone," when symptoms initially worsen, and add prednisone 0.5 mg/kg if symptoms enter the "red zone," when breathlessness is present at rest or with activities of daily living. (Level of evidence = 1b)

Boushey HA, Sorkness CA, King TS, et al, for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med*. 2005;352:1519-1528.

Synopsis One of the things that primary care physicians are frequently criticized for is a failure to treat asthma patients as intensively as is recommended by some guidelines. For example, adults with mild persistent asthma (self-treatment with beta-agonist more than 2 days per week, nighttime awakenings related to asthma more than 2 days per month, or variability in the peak expiratory flow of 20% to 30%) should be taking chronic anti-inflammatory medications based on current National Heart, Lung, and Blood Institute guidelines. Or should they? After an active run-in period, adults with this severity of asthma were randomized (allocation uncertain) to receive either

200 mcg of inhaled budesonide (Pulmicort) twice daily, 20 mg of oral zafirlukast (Accolate) twice daily, or matching placebo. All groups could use rescue therapy with budesonide, as needed, according to a symptom guide, as well as inhaled albuterol (salbutamol). They were followed up for 1 year with a variety of symptoms scores and physiologic measures. Follow-up was good, with 199 of 225 patients completing the study. After 1 year, patients in the placebo group (intermittent therapy only) performed slightly worse on a number of outcome measures, such as exhaled nitric oxide levels and the percentage of eosinophils in the sputum. There was no difference regarding the primary outcome of morning peak expiratory flow. If you understand the difference between patient- and disease-oriented outcomes, you should say to yourself, "Who cares?" More important, there was no clinically significant difference in the number of courses of budesonide or asthma control scores (0.1 to 0.2 on a 6-point scale), and no difference in quality of life scores.

Gabapentin + morphine marginally better than either alone for neuralgia

Clinical question Is the combination of gabapentin (Neurontin) and morphine more effective for neuropathic pain than either drug alone?

Bottom line The combination of gabapentin and morphine provides a small but clinically unimportant benefit over either drug alone. Tricyclic antidepressants have been shown in other studies to be as effective as gabapentin and much less expensive but were not studied in this trial. (Level of evidence = 1b)

Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;52:1324-1334.

Synopsis Gabapentin (Neurontin) and morphine are widely used for neuropathic pain, but it is unclear whether the combination is better than either drug alone. This small study used a crossover design: Each patient took each drug or combination of drugs and served as his or her own control. This study design makes it possible to identify statistically significant results with a relatively small sample size. The 57 patients in the study had diabetic neuropathy or postherpetic neuralgia that was at least moderate in severity and had been present for at least 3 months. Those with postherpetic neuralgia were somewhat older than those with diabetic neuropathy (mean age = 68 versus 60 years). They stopped taking any medications for neuralgia and kept a pain diary for 7 days to establish their baseline level of symptoms. Patients were then randomly assigned (allocation concealed) to 1 of 4 treatment sequences. Each sequence included the following maximal target doses for the 4 treatment regimens: (1) sustained release morphine, 60 mg twice daily, (2) gabapentin, 3,200 mg daily in 3 divided doses, (3) sustained-release morphine, 30 mg twice daily plus gabapentin, 800 mg 3 times daily, and (4) active placebo with a low dose of lorazepam (not believed to be effective for neuropathic pain but more likely to fool patients into thinking they were taking an active drug because of its side effects). Each treatment period was 5 weeks long, with the dose slowly escalated during the first 3 weeks, outcomes measured during the fourth week, and the drugs tapered and stopped during the fifth week. Older and smaller patients had somewhat lower target doses than the doses given above (60 mg for morphine alone and 2,400 mg for gabapentin alone). In fact, most patients did not reach the maximal dose; the mean final doses for morphine and gabapentin when used in combination were 35 mg and 1,700 mg per day, respectively.

Only 41 of 57 patients completed the study, most dropping out during the first treatment period. The primary outcome was the mean pain intensity on a scale from 0 to 10 during the fourth

week when patients were receiving the maximal dose of each drug. Average pain intensity was 5.7 at baseline and was decreased to 4.5 with placebo, 4.15 with gabapentin, 3.7 with morphine, and 3.1 with the combination of gabapentin and morphine. The differences between the individual active drugs and the combination was statistically significant but of marginal clinical significance. In general, on a 10-point scale, a difference of less than 1 point to 1.5 points is not clinically important. Patients receiving morphine either alone or in combination with gabapentin had significant side effects: 21% receiving the combination had constipation, sedation, and dry mouth.

Diuretics the first choice in hypertensive blacks and nonblacks

Clinical question What class of drugs are the best initial agents for the treatment of hypertension in black and nonblack patients?

Bottom line Thiazide-type diuretics are the best initial agents for the treatment of hypertension for most patients, including both blacks and nonblacks. (Level of evidence = 1b)

Wright JT, Dunn JK, Cutler JA, et al, for the ALLHAT Collaborative Research Group. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA*. 2005;293:1595-1608.

Synopsis Although evidence supports diuretics as the initial agent for most patients with hypertension, few outcome data are available specifically for blacks with hypertension. The authors report a prespecified subgroup analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a large, randomized, double-blind, controlled trial conducted between 1994 and 2002. ALLHAT included 33,357 hypertensive patients (35% black) 55 years or older with at least 1 other cardiovascular risk factor. Subjects were randomly assigned (uncertain allocation concealment) to initial therapy with a calcium channel blocker (amlodipine [Norvasc]), an angiotensin-converting enzyme inhibitor (lisinopril [Prinivil]), or a thiazide-type diuretic (chlorthalidone [Hygroton]). Other medications were added to achieve a blood pressure goal of lower than 140/90 mm Hg. Follow-up occurred for an average of 5.7 years for 97% of the subjects. Individuals blinded to treatment group assignment assessed reported outcomes. Using intention-to-treat analysis, both black and nonblack patients receiving amlodipine instead of chlorthalidone had an increased risk of heart failure (blacks: number needed to treat to harm [NNTH] for 6 years = 32; 95% CI, 20-61; nonblacks: NNTH for 6 years = 38; 25-72) with no difference in treatment effect by race. Black patients receiving lisinopril instead of chlorthalidone also had an increased risk of both stroke and combined cardiovascular disease morbidity/mortality (coronary heart disease death, nonfatal myocardial infarction, stroke, angina, coronary revascularization, heart failure, or peripheral vascular disease).

Diagnosis unaffected by giving kids narcotics for abdominal pain

Clinical question Does giving a narcotic to children with abdominal pain obscure the surgical diagnosis?

Bottom line Giving analgesics to children with abdominal pain does not obscure the surgical diagnosis. We don't need to make kids suffer while waiting for a surgeon to evaluate their abdominal pain. (Level of evidence = 2b)

Kokki H, Lintula H, Vanamo K, et al. Oxycodone vs placebo in children with undifferentiated abdominal pain: a randomized, double-blind clinical trial of the effect of analgesia on diagnostic accuracy. *Arch Pediatr Adolesc Med*. 2005;159:320-325.

Synopsis These researchers enrolled children aged 4 years to 15 years who came to the emergency department with acute abdominal pain of less than 7 days' duration and had pain scores of 5 cm or higher on a 10-cm visual analog scale.

The children were randomly assigned (concealed allocation) to receive oxycodone buccally (0.1 mg/kg) or placebo. The 63 children were asked to rate their pain every 30 minutes for up to 3.5 hours after treatment. One of 3 study surgeons evaluated each child, provided a provisional diagnosis (appendicitis, nonspecific abdominal pain, or other), a differential diagnosis, and initial management (observation or surgery), and assessed whether there was abdominal guarding. The same surgeon re-examined the patient 1 hour after the first dose of the study drug and provided the same assessments as at baseline. Researchers contacted the children with nonspecific abdominal pain 4 weeks later. The main outcomes were pain intensity difference, the presence of abdominal guarding before and after medication, and the diagnostic accuracy between the oxycodone and placebo groups. The authors don't say if these were assessed via intention to treat. The children receiving oxycodone began experiencing pain relief within the first 30 minutes. The diagnostic accuracy was not adversely affected by the administration of the drug. The study was powerful enough to detect modest differences in pain intensity.

ASA prevents stroke, not MI, in women

Clinical question Does aspirin prevent cardiovascular disease in women?

Bottom line Aspirin reduces the risk of stroke and transient ischemic attack in women but does not reduce the risk of MI or cardiovascular (CV) death. The reduction in strokes over 10 years (number needed to treat = 444) must be balanced against an increase in serious GI bleeds (number needed to treat to harm = 553). No change was seen in this large, long study regarding all-cause mortality. (Level of evidence = 1b)

Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352:1293-1304.

Synopsis Most data on aspirin for the prevention of CV events come from studies in men. The current study represents the largest and best evidence to date for women. Women older than 45 years without a history of coronary artery disease, cerebrovascular disease, or cancer were initially enrolled in a 3-month placebo run-in period to establish compliance with the study protocol. Those who complied (n = 39,876) were randomized to receive either 100 mg aspirin daily or placebo. They were followed up for a mean of 10 years, with 97% complete data on morbidity and 99% complete data on mortality. The mean age was 55 years, and the 10-year risk of heart disease was less than 5% in 85% of the women. Groups were balanced at the start of the study, outcomes were blindly assessed, and analysis was by intention to treat. Women taking aspirin were less likely to have a stroke (1.1% versus 1.3%; $P=.04$; number needed to treat [NNT] = 444 for 10 years) or transient ischemic attack (0.9% versus 1.2%; $P=.01$; NNT = 384 for 10 years) than women taking placebo. However, there were no differences between groups in the likelihood of MI (0.99% for aspirin and 0.97% for placebo) or death from CV causes (0.6% versus 0.63%), any major cardiovascular event (2.4% versus 2.6%), or any cause (3.1% versus 3.2%). GI bleeds requiring transfusion were more common in the aspirin group (0.64% versus 0.46%; $P=.02$; number needed to treat to harm = 553 for 10 years). The study was powered to have an 86% chance to detect a 25% reduction in the primary outcome of any major CV event. Review of the survival curve reveals a steady but small trend in favor of aspirin regarding the primary outcome. This apparent benefit, equivalent to a 5% to 10% relative reduction in all-cause mortality, was not statistically significant despite the study's large size.

Levels of evidence are explained at <http://www.infopeoms.com/levels.html>.

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