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STUDY LEVELS OF EVIDENCE (LOE)

From the Centre for Evidence-Based Medicine, Oxford. For the most up-to-date levels of evidence, see www.cebm.net/levels_of_evidence.asp

Therapy/Prevention/Etiology/Harm:

- 1a: Systematic reviews of randomized controlled trials
- 1b: Individual randomized controlled trials
- 1c: All or none randomized controlled trials
- 2a: Systematic reviews of cohort studies
- 2b: Individual cohort study or low-quality randomized controlled
- 2c: "Outcomes" research, ecological studies

Diagnosis:

- 1a: Systematic review of level-1 diagnostic studies
- 1b: Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard, or a clinical decision rule not validated on a second set of patients
- 1c: Absolute SpPins and SnNouts
- 2a: Systematic review of level >2
- 2b: Independent blind or objective comparison, study confined to a narrow spectrum of study individuals, or a diagnostic clinical rule not validated in a test set

Prognosis:

- 1a: Systematic review of inception cohort studies
- 1b: Individual inception cohort study with >80% follow-up, or a clinical rule not validated on a second set of patients
- 1c: All or none case series
- 2a: Systematic review of either retrospective cohort studies or untreated control groups in RCTs
- 2b: Retrospective cohort study or follow-up of untreated control patients in an RCT, or clinical rule not validated in a test set
- 2c: "Outcomes" research

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Vitamin D, at High Doses, Prevents Fractures

Clinical Question

Can vitamin D prevent important fractures related to osteoporosis?

Bottom Line

Vitamin D at dosages greater than 400 IU per day is effective in decreasing nonvertebral fractures, including hip fractures. The effect is dose dependent; dosages less than 400 IU per day are ineffective. A practical way to implement this low-cost approach is to suggest nonprescription vitamin D supplements at dosages of 800 IU per day; that way, missed doses will still keep the average daily dose in the range of effectiveness. (LOE = 1a)

Study Design

Meta-analysis (randomized controlled trials)

Funding

Foundation

Setting

Various (meta-analysis)

Synopsis

This meta-analysis, now the fourth on this topic in the past 5 years, went further than the other ones and looked at the relationship of dose and effectiveness of vitamin D in preventing nonvertebral fractures, especially hip fracture. To identify articles, the authors searched 3 databases, including the Cochrane Controlled Trials Register, and searched meeting abstracts and reference lists of identified articles, and contacted experts in the field. They identified 12 double-blind randomized controlled trials (enrolling a total of 42279 patients with an average

age of 78 years) that included data on how the fractures happened and data regarding adherence so they could calculate the received dosage of vitamin D. Data from the studies were independently abstracted by 3 researchers, then compared. Combining all trials, vitamin D supplementation produced a small decrease in nonvertebral fractures (relative risk, 0.86; 95% CI, 0.77-0.96). However, the results across studies were heterogeneous until they stratified study results by dosage. Dosages of 400 IU per day or less did not reduce nonvertebral fracture risk. Dosages of greater than 400 IU per day significantly reduced nonvertebral fractures, with 1 fracture prevented for every 93 patients treated with vitamin D instead of placebo for 12 months to 84 months (number needed to treat [NNT] = 93; 66-160). The effect was more pronounced with cholecalciferol (vitamin D3) than with ergocalciferol (vitamin D2). Similarly, hip fractures were also prevented by higher dosages of vitamin D (NNT = 202; 114-823). The addition of calcium supplementation did not improve results.

REFERENCE

Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D dose dependency. A meta-analysis of randomized controlled trials. *Arch Intern Med.* 2009;169(6):551-561.

Treatment of Periodontal Disease in Pregnancy Reduces Preterm Birth?

Clinical Question

Does the treatment of periodontal disease in pregnancy reduce the risk of preterm birth?

Bottom Line

Women with periodontal disease in pregnancy should be treated to reduce the risk of preterm birth. (LOE = 1a)

Study Design

Meta-analysis (randomized controlled trials)

Funding

Unknown/not stated

Setting

Various (meta-analysis)

Synopsis

This meta-analysis of randomized controlled trials included 7 studies with a total of 2663 pregnant women with gingivitis or periodontitis, according to the definitions of the International Workshop for a Classification of Periodontal Diseases and Conditions in 1999. The authors identified studies comparing the effects on birth outcomes of treatment using scaling and/or root planing vs no treatment. Treated women had a lower incidence of preterm birth (odds ratio [OR], 0.55; 95% CI, 0.35-0.86.) Low birth weight was reported in 5 of the studies, and reduction with treatment was of borderline statistical significance (OR, 0.48; 95% CI, 0.23-1.00; $P = .49$). The difference in abortion/stillbirth reported in 4 studies was not significantly different (OR, 0.73; 95% CI, 0.41-1.31).

REFERENCE

Polyzos NP, Polyzos IP, Mauri D, et al. Effect of periodontal disease treatment during pregnancy on preterm birth incidence: a meta-analysis of randomized trials. *Am J Obstet Gynecol*. 2009;200(3):225-232.

Escitalopram, Sertraline More Effective, Better Tolerated Than Other Newer Antidepressants
Clinical Question

In head-to-head studies of new-generation antidepressants, which are more effective?

Bottom Line

In studies directly comparing newer antidepressants, escitalopram and sertraline are generally more effective and better tolerated. Keep in mind that in placebo-controlled trials, none of the antidepressants seem all that impressive. (LOE = 1a-)

Study Design

Meta-analysis (randomized controlled trials)

Funding

Self-funded or unfunded

Setting

Various (meta-analysis)

Synopsis

These authors, most of whom have ties to several pharmaceutical companies, searched the Cochrane registers to identify randomized trials comparing new-generation antidepressants (basically anything other than tricyclic antidepressants and monoamine oxidase inhibitors) with one another during the first 8 weeks of treating adults with depression. They excluded placebo-controlled studies. Although head-to-head studies are the best way to compare effectiveness, keep in mind that most studies of antidepressants have found them to be minimally more effective than placebo. Two investigators independently assessed study eligibility and study quality. The authors included 117 randomized trials, including nearly 26 000 patients. Because there was a wide range of doses used in the studies, the authors tried to assess

comparability of doses. The main outcomes of interest were response (defined as a 50% improvement or more in depression scores) and all-cause dropouts. When comparing drugs A, B, and C, it is possible to have odd results such as A is better than B, B is better than C (suggesting that A is also better than C), but C is better than A. The authors used fairly complex approaches to make certain that the comparisons do not disagree by chance. They found the data were fairly heterogeneous across studies. In general, there were no meaningful differences in effectiveness and tolerability among the various agents. The following present nonrandom findings in alphabetical order: bupropion (Wellbutrin) was more effective and better tolerated than reboxetine. Citalopram (Celexa) was more effective than reboxetine and better tolerated than fluvoxamine and reboxetine. Duloxetine (Cymbalta) was slightly less effective than escitalopram, mirtazapine, and venlafaxine. It was more effective than reboxetine and was less tolerable than escitalopram and sertraline. Escitalopram (Lexapro) was more effective than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. It was tolerated better than duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine. Fluoxetine (Prozac) was slightly less effective than escitalopram, mirtazapine, sertraline, and venlafaxine. It was more effective and better tolerated than reboxetine. Fluvoxamine (Luvox) was slightly less effective than escitalopram, mirtazapine, and venlafaxine. It was more effective than reboxetine. It was less tolerable than citalopram, escitalopram, and sertraline. Milnacipran (Savella) was more effective than reboxetine. Mirtazapine (Remeron) was more effective than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. Paroxetine (Paxil) was less effective than escitalopram, mirtazapine, sertraline, and venlafaxine. It

was more effective than reboxetine. It was less tolerable than escitalopram and sertraline. Reboxetine (Edronax, Vestra) was less effective than every drug against which it was compared and was less tolerable than most of the comparators. Sertraline (Zoloft) was more effective than fluoxetine, paroxetine, and paroxetine. It was better tolerated than duloxetine, fluvoxamine, paroxetine, and reboxetine. Venlafaxine (Effexor) was more effective than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine. It was slightly less tolerable than escitalopram. The authors point out the evidence of bias in favor of commercially sponsored studies and that many of the newest medications (mirtazapine, escitalopram, bupropion, and duloxetine) may especially benefit from this.

REFERENCE

Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet*. 2009;373(9665):746-758.

Early Treatment for PTSD

Clinical Question

Is early treatment after a traumatic stress event beneficial?

Bottom Line

Identification of a traumatic stress event within 3 months and treatment using trauma-focused cognitive behavioral therapy is beneficial for patients who meet criteria from the *Diagnostic and Statistical Manual, Fourth Edition* for the diagnosis of posttraumatic stress disorder (PTSD). It is uncertain whether individuals would benefit if they are symptomatic but do not meet diagnostic criteria for PTSD. (LOE = 1a-)

Study Design

Meta-analysis (randomized controlled trials)

Funding

Unknown/not stated

Setting

Various (meta-analysis)

Synopsis

This is a meta-analysis of randomized controlled trials of psychological interventions (of more than 1 session) to reduce traumatic stress symptoms within 3 months of a traumatic stress event compared with placebo or other control (eg, waiting list or usual care). The authors identified 25 studies that met inclusion criteria. Intervention for individuals involved in a traumatic event irrespective of symptoms showed no difference between any intervention and control groups. Among individuals with traumatic stress symptoms irrespective of symptoms, trauma-focused cognitive behavioral therapy (CBT) was more effective than waiting list or supportive counseling (relative risk [RR], 0.72; 95% CI, 0.50-1.05), especially those meeting criteria for diagnosis of PTSD (RR, 0.54; 0.31-0.95). Trauma-focused CBT was defined as "any intervention that focused on the trauma using exposure to trauma memories and trauma reminders with or without cognitive therapy and other cognitive-behavioral techniques."

REFERENCE

Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI. Systematic review and meta-analysis of multiple session early interventions following traumatic events. *Am J Psychiatry*. 2009;166(3):293-301.

Barley Lowers Total and LDL Cholesterol, No Effect on HDL

Clinical Question

Does barley improve cholesterol levels?

Bottom Line

Overall, barley lowers total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels and

has no effect on high-density lipoprotein cholesterol (HDL-C) levels. When used in patients with hypercholesterolemia, however, barley was no better than control. Keep in mind that in studies of other interventions, lowering cholesterol levels did not always lead to a reduction in clinical events. (LOE = 1a-)

Study Design

Meta-analysis (randomized controlled trials)

Funding

Unknown/not stated

Setting

Various (meta-analysis)

Synopsis

These authors searched multiple databases to find randomized trials that studied barley's effects on cholesterol. Although they do not describe searching for unpublished data, they assessed the potential presence of publication bias. Two researchers independently assessed study eligibility and extracted data. They do not describe assessing the quality of the individual studies. They ultimately included 8 small studies with a total of 391 patients. In these studies, barley was administered as the grain or as a concentrate. Six of the studies evaluated patients with hypercholesterolemia; the other 2 evaluated healthy patients. Only 2 were double-masked studies. One study lasted 12 weeks; the rest lasted 4 weeks to 6 weeks. Overall, compared with control, barley lowered the total cholesterol level by 13 mg/dL (0.3 mmol/L), LDL-C by 10 mg/dL (0.26 mmol/L), and triglycerides by 11.8 mg/dL (0.13 mmol/L), but had no effect on HDL cholesterol. The authors did all kinds of analyses to see if study design factors, patient factors (healthy patients vs those with hypercholesterolemia), and cointerventions made any difference. These other factors did not have much effect except in patients

with hypercholesterolemia in whom barley was no better than control. The authors' analysis did not raise concerns for the presence of publication bias.

REFERENCE

Talati R, Baker WL, Pablonia MS, White CM, Coleman CI. The effects of barley-derived soluble fiber on serum lipids. *Ann Fam Med*. 2009;7(2):157-163.

All Diets Work Equally Poorly

Clinical Question

What is the most effective diet for weight loss?

Bottom Line

This largest, most carefully designed, and longest study to date of different diets showed that it does not really matter which one you choose. Rather, motivation (for which attendance at group sessions can be considered paramount) and sticking to the diet are most important. It is also important to remember that the goal of any diet should be not only to lose weight but to maintain or improve health. (LOE = 1b)

Study Design

Randomized controlled trial (double-blinded)

Funding

Government

Allocation

Concealed

Setting

Population-based

Synopsis

Previous studies of diet have been limited by small size, short duration, lack of masking, and significant loss to follow-up. This study attempted to address those limitations by randomizing 811 overweight persons (body mass index [BMI] 25-40 kg/m²) to 1 of 4 diets: (1) low fat, average protein; (2) low fat, high protein; (3) high fat, average protein; and (4) high fat, high protein. The percentage of carbohydrates ranged from 35% to 65% within the 4 diets. Comparisons could therefore be made between high and low protein, fat, and carbohydrate diets. Patients were given menus with similar foods but differing in the macronutrient content as described above, to preserve masking. Each diet was designed to deliver a 750-calorie net deficit compared with what they need to maintain their current weight. Group sessions were held 3 times per month for 6 months, then twice each month for the remaining 18 months of the study. Participants were asked to exercise 90 minutes per week. Patients with diabetes, unstable heart disease, or poor motivation as determined by an intake questionnaire were excluded.

Thus, many of the patients we need to help were excluded (ie, obese, unmotivated diabetics). Groups were balanced; the average age of participants was 51 years; 64% were women; 79% were white; and the mean BMI was 33 kg/m². At 6 months, participants in all 4 groups had lost an average of 6 kg. However, they began to regain weight 6 months later, and by 24 months the average weight loss was between 2.9 kg and 3.6 kg in each group in the intention-to-treat analysis. There was no difference between groups. Similarly, patients in each group lost approximately 4 cm in waist size. One of the best predictors of success was showing up at the group sessions. Overall, though, patients were similar satisfied with the diets and reported similar levels of fullness, hunger, and craving. There were minor differences in cardiovascular risk factors between baseline and the end of the study, notably a greater decrease in LDL-C in the low-fat and high-carbohydrate groups than in the low-carbohydrate or high-fat groups, and a greater increase in HDL-C in the low-carbohydrate group. Greater weight loss and persistence of weight loss was seen in adherent patients.

REFERENCE

Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med*. 2009;360(9):859-873.