POEMs

For definitions of levels of evidence used in POEMs, see http://www.essentialevidenceplus.com/product/ebm_loe.cfm?show=oxford.

To subscribe to a free podcast of these and other POEMs that appear in *AFP,* search in iTunes for "POEM of the Week" or go to http://goo.gl/3niWXb.

This series is coordinated by Sumi Sexton, MD, Associate Deputy Editor.

A collection of POEMs published in *AFP* is available at http://www.aafp.org/afp/poems.

CBT Effective in Adolescents with Depression Who Do Not Want Medication

Clinical Question

Is cognitive behavior therapy (CBT) effective for adolescents with depression who decline antidepressant drug treatment?

Bottom Line

In adolescents who eschew drug treatment of major depression, short-term CBT is more effective than treatment as usual in inducing recovery, with a number needed to treat of 4 to 10. CBT also produced faster results. (Level of Evidence = 1b)

Synopsis

These researchers identified potential patients by mailing study brochures to parents of adolescents 12 to 18 years of age who had a recent prescription for an antidepressant (from a health maintenance organization in the United States) that went unfilled or was initially dispensed but not refilled. In other words, the patients did not fail antidepressant therapy but simply chose not to begin (or continue) it. The 212 adolescents who had major depressive disorder were randomized (allocation concealment uncertain) to continue treatment as usual (as determined by their primary care clinician) or treatment as usual plus at least four sessions of CBT aimed at addressing unrealistic thinking and increasing pleasant activities (behavioral activation). The patients could continue a second set of four to six sessions, if desired, and most did. Recovery, defined as at least eight weeks of well time as measured by the Children's Depression Rating Scale—Revised, occurred significantly faster in the CBT group and was significantly more likely in the first year but not the second year of follow-up. Quality of life was better with therapy in the first year after therapy but not in the second year. Hospital admissions for psychiatric diagnoses were significantly higher in the control group. Substance use, suicidal behavior, and parent-reported outcomes were not different between the two groups, but the study may not have been long enough to find a difference, if one exists. These results agree with the results of several meta-analyses examining the effect of CBT for adolescents with depression.

Study design: Randomized controlled trial (nonblinded)

Funding source: Government

Allocation: Uncertain

Setting: Outpatient (primary care)

Reference: *Clarke G, DeBar LL, Pearson JA, et al. Cognitive behavioral therapy in primary care for youth declining antidepressants: a randomized trial.* Pediatrics. *2016;137(5):e20151851.*

ALLEN F. SHAUGHNESSY, PharmD, MMedEd
Professor of Family Medicine
Tufts University
Boston, Mass.

Flibanserin Ineffective for Hypoactive Sexual Desire Disorder in Women

Clinical Question

Is flibanserin (Addyi) a safe and effective treatment of hypoactive sexual desire disorder in premenopausal women?

Bottom Line

Flibanserin produces a minimal effect on sexual desire and minimally increases the number of satisfying sexual events in women ▶

(less than one-half an event per month increase). Many women will be unable to tolerate the adverse effects. (Level of Evidence = 1a)

Synopsis

To assemble studies for inclusion, these authors searched three trial registries and 13 electronic databases, including the Cochrane Library, with reference lists of retrieved articles to identify randomized studies. They included studies published in any language. Two researchers independently identified the studies for inclusion; data were extracted by one reviewer and checked by another. They included five published and three unpublished studies that enrolled a total of 5,914 premenopausal and postmenopausal women. The overall study quality was low: many women dropped out, some authors shifted end points mid-study, and some authors used the "last observation carried forward." Benefit was statistically significant but clinically minimal for most outcomes. On average across the studies, treatment, compared with placebo, resulted in one additional satisfying sexual event every two months. Diary scores for sexual desire increased from 1.7 to 2.3 points on a scale of 0 to 84 (four studies), and scores on the female sexual function index increased an average of 0.2 to 0.4 on a scale of 1.2 to 6.0. There was minimal or no change in the women's mean global impression of improvement. Patients who received treatment were twice as likely to drop out because of adverse effects, including dizziness, which was four times more likely in that group.

Study design: Meta-analysis (randomized controlled trial)

Funding source: Self-funded or unfunded

Setting: Various (meta-analysis)

Reference: *Jaspers L, Feys F, Bramer WM, Franco OH, Leusink P, Laan ET. Efficacy and safety of flibanserin for the treatment of hypoactive sexual desire disorder in women: a systematic review and meta-analysis.* JAMA Intern Med. *2016;176(4):453-462.*

ALLEN F. SHAUGHNESSY, PharmD, MMedEd
Professor of Family Medicine
Tufts University
Boston, Mass.

Newer Sulfonylureas Not Associated with Increased Mortality, MIs, or Strokes

Clinical Question

Are newer-generation sulfonylureas associated with bad outcomes in patients with type 2 diabetes mellitus?

Bottom Line

In multiple randomized trials, the long-term use of second- or third-generation sulfonylureas in patients with type 2 diabetes is not associated with more deaths, myocardial infarctions (MIs), or strokes. The included trials tended not to report other safety data. (Level of Evidence = 1a)

Synopsis

These authors reviewed two databases and the Cochrane Library to identify randomized trials of second- or third-generation sulfonylureas in patients with type 2 diabetes. Additionally, they searched for unpublished studies by looking at clinical trial registries and the abstracts of international diabetes meetings. The trials had to be at least one year in duration and evaluate all-cause or cardiovascular mortality. If reported in the included study, these authors also collected data on MIs and strokes. Because most of the trials were interested only in nearly meaningless markers of glycemic control, these outcomes were often missing (36 studies representing 10% of the patient pool), so the authors tried to contact the original study team to obtain the missing outcome data (five responded but provided no data). The authors also excluded studies that compared sulfonylureas with drugs that have been withdrawn from the market. Two of the authors independently assessed studies for inclusion and resolved disagreements by consensus, using a third party only when they could not agree. They also assessed each study's potential for bias. Finally, in addition to the usual statistical gymnastics, these authors did a "trial sequential analysis" that allows for the assessment of overall power as well as dampens the potential impact of multiple analyses.

Ultimately, they included 47 trials with approximately 38,000 patients but only 890 deaths. The trials lasted from 12 to 133 months and were generally of decent quality. In the end, the use of newer sulfonylureas was not associated with any statistically significant increase in all-cause mortality, cardiovascular mortality, MI, or stroke. When the authors restricted the analysis to studies that lasted at least two years, they found no difference. Finally, their trial sequential analysis suggested that the data are robust enough to detect at least a 0.5% absolute difference in outcomes, a value that would translate to a number needed to treat to harm of 200.

Study design: Meta-analysis (randomized controlled trial)

Funding source: Government

Setting: Various (meta-analysis)

Reference: *Rados DV, Pinto LC, Remonti LR, Leitão CB, Gross JL. The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials [published correction appears in* PLoS Med. *2016;13(6):e1002091].* PLoS Med. *2016;13(4):e1001992.*

HENRY C. BARRY, MD, MS
Professor
Michigan State University
East Lansing, Mich.

Inhaled Fluticasone/Salmeterol Better Than Fluticasone Alone for Moderate to Severe Asthma

Clinical Question

Is the combination of a long-acting beta agonist and an inhaled corticosteroid as safe and effective as an inhaled corticosteroid alone?

Bottom Line

The combination of fluticasone and salmeterol (Advair), with the steroid dose adjusted for disease severity, reduces the number of severe asthma exacerbations more than fluticasone (Flovent) alone (number needed to treat [NNT] = 50 over 26 weeks), with no difference in terms of potential harms, such as intubation or asthma-related death. (Level of Evidence = 1b)

Synopsis

This study was performed by GlaxoSmithKline at the behest of the U.S. Food and Drug Administration because of enduring concerns about the safety of long-acting beta agonists. The authors identified patients with moderate to severe asthma who had experienced at least one exacerbation in the previous year that required systemic steroids or hospitalization (but no such episode in the previous month). The 11,751 patients from 694 centers were randomized to receive fluticasone/salmeterol or fluticasone alone. The dose of fluticasone alone was stratified into three subgroups based on disease severity: 100 mcg, 250 mcg, and 500 mcg. In the combination treatment group, salmeterol (50 mcg) was combined with fluticasone at 100 mcg, 250 mcg, and 500 mcg, according to disease severity. All medications were given twice daily. Patients were 12 years and older (mean age = 43 years), and most patients were from North America or Europe. Groups were balanced at the beginning of the study, and analysis was by intention to treat. Outcomes were adjudicated by members of the research team who were masked to treatment assignment.

The primary efficacy end point was the first severe asthma exacerbation, defined as the use of systemic steroids for at least three days, asthma-related hospitalization, or an emergency department visit resulting in systemic steroid administration. There were fewer severe asthma exacerbations in the fluticasone/salmeterol group than in the group that received fluticasone alone (8% vs. 10%; $P < .001$; NNT = 50 over 26 weeks). The primary safety outcome (a composite of asthma-related deaths, asthma-related intubations, and asthma-related hospitalizations) was similar between groups: 36 events in the fluticasone/salmeterol group and 38 events in the fluticasone-only group. There were three deaths in the fluticasone/salmeterol group and six in the fluticasone-only group, none of which were adjudicated as being related to asthma.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Concealed

Setting: Outpatient (any)

Reference: *Stempel DA, Raphiou IH, Kral KM, et al.; AUSTRI Investigators. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone.* N Engl J Med. *2016;374(19):1822-1830.*

MARK H. EBELL, MD, MS
Professor
University of Georgia
Athens, Ga. ■