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EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

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FPIN
Family Physicians Inquiries Network

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EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

STATEMENT OF PURPOSE

Evidence-Based Practice (EBP) addresses important patient care questions asked by practicing family physicians, using the best sources of evidence in a brief, clinically useful format. Our goal is to instruct our authors on how to write peer-reviewed scholarly research for the medical and scientific community.

EDITORIAL POLICY

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DISCLOSURE

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Do statins for primary prevention improve outcomes in older adults?

CASE

A 76-year-old man presents for an annual wellness visit. He has no personal history of cardiovascular disease, although he notes his wife recently had a stroke. He feels he is a robust grandfather and wants to know what he can do to stay healthy and prevent or delay common causes of death in his age group. Does statin use for primary prevention reduce morbidity and mortality in older adults?

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Bottom Line

When used for primary prevention in older adults, statins decrease risk of cardiovascular events. Although a large retrospective cohort study demonstrated a reduction in all-cause mortality as soon as two years after initiation of a statin for primary prevention, meta-analyses of randomized controlled trials (RCTs) have not clearly demonstrated a mortality benefit.

Evidence Summary

A meta-analysis of 17 RCTs summarized the evidence for both primary and secondary prevention of cardiovascular disease in patients 65 years old and older.[1] The mean follow-up duration was 3.7 years. Seven RCTs (N=21,781) demonstrated a similar risk of composite cardiovascular events (myocardial infarction [MI], stroke, cardiovascular death, and revascularization) in patients on statin therapy for primary prevention compared with controls (odds ratio [OR] 0.88; 95% CI, 0.72–1.1). Four RCTs (N=14,821) demonstrated that statins used for primary prevention did not reduce all-cause mortality (OR 0.94; 95% CI, 0.76–1.2). Four RCTs (N=14,136) reported no significant effect of statins on primary prevention of cardiovascular mortality (OR 1.0; 95% CI, 0.81–1.2) but did show a significant reduction in the incidence of MI (OR 0.61; 95% CI, 0.50–0.73). Two RCTs (N=6,824) showed a reduced risk of revascularization with statin use for primary prevention (OR 0.49; 95% CI, 0.32–0.76). For primary prevention of stroke, six RCTs (N=19,189) showed a similar risk of stroke in the statin group compared with the control group (OR 0.78; 95% CI, 0.60–1.00). However, after further analysis and excluding studies with high risk of bias, the statin group was found to have a lower risk of stroke (OR 0.72; 95% CI, 0.54–0.95). This analysis suggests that statins used for primary prevention in the elderly may lower the risk of MI, revascularization, and stroke, but not lower cardiovascular or all-cause mortality. The safety of statin use was not evaluated.

A meta-analysis of two large RCTs evaluated the age-specific effect of statin initiation for primary prevention on the composite endpoint of nonfatal MI, nonfatal stroke, and cardiovascular death.[2] One of the trials was also included in the above meta-analysis. Interventions in both trials were rosuvastatin (20 or 10 mg), which is more reflective of current practice than some older trials. Among participants who were 70 years old or older, a 26% relative risk reduction was observed in the treatment group compared with the control group (n=8,781; hazard ratio [HR] 0.74; 95% CI, 0.61–0.91). A similar risk reduction was noted in adults 65 to 69 years old (n=8,208; HR 0.51; 95% CI, 0.38–0.69) and in adults <65 years old (n=13,517; HR 0.75; 95% CI, 0.57–0.97), and heterogeneity by age was not observed. Older participants experienced higher rates of cardiovascular events, with patients ≥70 years old representing 24% and 32% of the trial populations but experiencing 43% and 55% of the cardiovascular events, respectively. This would imply larger absolute rate reductions and smaller numbers needed to treat in older populations. All-cause mortality was reported as a separate endpoint for the RCTs individually, and neither showed a statistically significant reduction in mortality in patients ≥70 years old. Notably, rates of drug withdrawal among patients ≥70 years old in the statin groups were 21.6% and 29.1%, which were higher than in younger age groups.

A retrospective cohort study of veterans 75 years old and older (n=326,981) evaluated statin initiation and all-cause mortality, cardiovascular mortality, and composite cardiovascular events (myocardial infarction, stroke, and revascularization).[3] A total of 57,178 veterans (17%) initiated statins during the study period. Patients were primarily male (97%) and White (91%). Patients with a history of atherosclerotic cardiovascular disease or prior statin use were excluded, whereas those with cancer, dementia, or paralysis were included. The mean follow-up was 6.8 years. The authors used a propensity score analysis to minimize bias although unmeasured variables are an inherent risk with this study design. Statin use was associated with lower all-cause

mortality (HR 0.75; 95% CI, 0.74–0.76), lower cardiovascular mortality (HR 0.80; 95% CI, 0.78–0.81), and fewer composite cardiovascular events (HR 0.92; 95% CI, 0.91–0.94) compared with nonuse. Notably, the study observed benefit in all-cause mortality as soon as two years from statin initiation (HR 0.68; 95% CI, 0.66–0.69) with significantly reduced all-cause mortality for up to 6 years (HR 0.87; 95% CI, 0.84–0.91), but which became nonsignificant at eight years. A similar pattern for cardiovascular mortality was observed. An all-cause and cardiovascular mortality benefit was observed even in those 90 years old and older. The most common statin was simvastatin, which may underestimate the effect size compared with high-intensity statins.

CASE CONCLUSION

You explain to the patient that statins continue to reduce the risk of cardiovascular events in older adults, but they do not clearly alter longevity. After seeing what his wife went through with the stroke, he is strongly motivated to reduce his personal risk of that illness. Together, you decide to begin the patient on rosuvastatin 10 mg once daily. EBP

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3. Orkaby AR, Driver JA, Ho YL, et al. Association of statin use with all-cause and cardiovascular mortality in US veterans 75 years and older. *JAMA*. 2020;324(1):68-78. [STEP 3]

How does EMR implementation impact provider efficiency?

EVIDENCE-BASED ANSWER

The costs of implementing electronic medical record are substantial, and total average labor cost per patient increases at two months after implementation, without returning to baseline until six months postimplementation (SOR: **C**, usual practice). Although physicians perceive overall increases in access and communication, increased time is spent documenting and less time interacting with patients (SOR: **C**, usual practice).

DOI 10.1097/EBP.0000000000001610

A 2018 time-driven activity-based costing study examined the impact of electronic medical record (EMR) implementation on providers at two orthopedic clinics (n=143 patients).[1] Patients' demographics were not provided, but only patients who were being seen for suspected arthritis of the hip or knee, were scheduled to receive intra-articular injection into native knees, preop total knee arthroplasty (TKA) visits, or who had already undergone a TKA were included. Patients were prospectively hand-timed during their clinic visit, and the time spent with each provider including the attending surgeon, mid-levels such as physician assistants, technicians, and receptionists from the start to finish during one of four data collection periods was recorded. Researcher collected data including pre-implementation of the EMR (n=48), two to three months after health-system-wide implementation of EMR (n=33), six months (n=31), and two years postimplementation (n=31). The labor costs were calculated based on the average time in minutes spent by each provider multiplied by the cost rate of each staff member performing activities. Total labor costs per patient significantly increased from pre-EMR to two months post-EMR implementation ($135.66/min vs $179.17/min, $P=.05$), whereas no significant differences were noted at six months and two years. Providers spent more time per patient at all postimplementation time points (pre-EMR, 3.28 minutes; 2 months, 7.63 minutes; 6 months, 8.43 minutes; 2 years, 5.34 minutes; $P<.001$ between pre-EMR and 2 months), with assistant providers spending at least twice as long documenting encounters at two months after implementation as they had before implementation (pre-EMR, 3.44 minutes; 2 months, 9.14 minutes; 6 months, 6.69 minutes; 2 years, 6.12 minutes; $P<.001$ between pre-EMR and 2 months). A significant decrease was observed in average clinic volume from 84.5 to 60 patients per week for one clinic, which persisted at all time points after implementation ($P<.01$). The second clinics returned to similar weekly patient volume as pre-implementation (70 patients) at six months. This study was limited by the inability to measure true costs, the accuracy of timed data that was gathered, and lack of data on the quality of care and documentation.

A 2005 time–motion study observed the time differences between performing routine clinic activities pre-EMR and post-EMR implantation at five ambulatory primary care clinics (with 20 physicians).[2] Physicians were 75% female with a mean of 13.4 years in practice before EMR implementation. All physicians were offered one-hour personal training session, which was not mandatory. Residents and fellows were excluded from the study. Of 20 physicians, 16 were observed before implementation for a mean of 3.3 months, in addition to postimplementation for seven months, with four observed only postimplementation. Physicians were followed by observers during their entire clinic session and were directly timed while performing specific physician activities. Once observations were completed, participants were given a survey assessing each physician's estimates of the amount of time spent documenting outside of the clinic session, as well as grading quality measures including but not limited to overall satisfaction with the EMR, and if quality of care was impeded or enhanced. After longitudinal EMR implementation, physicians were still permitted to hand write or dictate notes and prescriptions, as well as use the EMR for these tasks. No significant difference was noted in adjusted mean overall time spent per patient between preintervention and postintervention (mean difference 0.5 min; 95% CI, –5.05 to 6.04, $P=.86$). A significant increase was noted in the amount of reading performed in support of patient care postimplementation (2.2 vs 3.1 minutes; $P=.029$). Thirteen physicians reported that more time was spent documenting postimplementation compared with seven who reported no change in time or less time was spent documenting. Improvement was noted in overall quality, access, and communication; however,

impact on workload was rated below neutral. No significant time shift in physician administrative duties was observed during postimplementation clinic sessions. Limitations included all participating clinics being associated within a single institution and the physicians were all volunteers and salaried general internists with productivity-based incentives, which may have influenced the results of the study. EBP

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Can shared decision-making help African Americans with asthma BREATHE better?

George M, Bruzzese JM, Lynn S Sommers M, et al. Group-randomized trial of tailored brief shared decision-making to improve asthma control in urban black adults. J Adv Nurs. 2021;77(3):1501-1517. doi: 10.1111/jan.14646

DOI 10.1097/EBP.0000000000001581

This group-randomized control trial piloted a shared decision-making intervention (BREATHE) to dose-matched attention control among 80 African Americans adults with uncontrolled persistent asthma. BREATH is a motivational interviewing and shared-decision making intervention with a one-time discussion delivered by clinicians during routine office visits to improve adherence with inhaled corticosteroids (ICSs). Providers underwent a two-hour training session. In the BREATHE group, clinicians used various media to prompt patients through the intervention during a seven-minute education. In the dose-matched attention control group, clinicians were trained using a self-guided manual that took about 10 minutes. In this group, patient discussion was unscripted and focused on healthy lifestyle. Primary outcome was mean score on the Asthma Control Questionnaire (ACQ), where a minimal clinically important difference of 0.5 has been established. Secondary outcomes included ICS adherence, quality of life, lung function, and symptom burden, evaluating feasibility and acceptability of the intervention.

Patients were an average 45 years old, over 80% were women, over 90% identified as Black, and virtually all patients were on a form of government insurance. In general, patients in the intervention group seemed to have worse control at baseline. The authors aimed to show differences between the groups; however, no significant differences were seen. Because of this, they reported differences within each group. BREATHE participants had better ACQ scores than their baseline during each timepoint of the three-month trial and the minimal clinically important difference was met at each point. A mean baseline score of 2.94 was noted with a reduction to 2.17 in month one, 2.22 in month two, and 2.40 in month three. Scores also improved in the control group but did not meet the clinically important standard; mean baseline score of 2.63 with a reduction to 2.16 in month one, 2.35 in month two, and 2.24 in month three. BREATHE participants also had fewer symptoms at follow-up (fewer nights woken, less shortness of breath, and less severity of symptoms) compared with baseline.

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	No	Implementable	No
Change in practice	Yes	Clinically meaningful	No

Bottom line: BREATHE is a brief tailored office-based intervention that can improve asthma outcomes in a high-risk vulnerable population of African American adults. No difference was seen for between patients randomized to BREATHE and those in the comparator group. Although challenges to validity and implementation are observed, both groups improved in asthma control, perhaps indicating that extra time spent discussing healthy interventions with patients is valuable.

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Adding metronidazole to treat PID

Wiesenfeld HC, Meyn LA, Darville T, Macio IS, Hillier SL. A Randomized Controlled Trial of Ceftriaxone and Doxycycline, With or Without Metronidazole, for the Treatment of Acute Pelvic Inflammatory Disease. Clin Infect Dis. 2021; 72(7):1181-1189. doi:10.1093/cid/ciaa101

DOI 10.1097/EBP.0000000000001640

In this randomized controlled trial conducted from November 2010 to January 2015, women 15 to 40 years old diagnosed with pelvic inflammatory disease (PID) were randomized to receive 14 days of metronidazole

500 mg twice daily or placebo. All patients received standard treatment of ceftriaxone 250 mg IM once daily and doxycycline 100 mg twice daily for 14 days. Patients were recruited from two emergency rooms and a county health department sexually transmitted infection clinic if they complained of lower abdominal or pelvic pain and had cervical motion tenderness, uterine tenderness, or tenderness of either right or left adnexa on pelvic examination. Exclusion criteria included pregnancy, need for inpatient treatment, use of systemic or intravaginal antibiotics within seven days, allergy to study drugs, an intrauterine procedure or miscarriage within six weeks, hysterectomy, or menopause. The primary outcome was clinical improvement at three-day follow-up as defined by a reduction in the clinical tenderness score. Secondary outcomes included presence of anaerobic organisms in endometrial aspirate at 30 days and "clinical cure" defined as absence of fever and >70% improvement in clinical tenderness at 30 days.

A total 233 patients were included in the intention-to-treat analysis; 116 patients in the treatment group and 117 in the placebo group. Ten patients were lost to follow-up at the 30-day evaluation in the treatment group and nine were lost in the placebo group. Most women were between 20 and 28 years old and a majority were black. No significant difference was noted in the primary outcome between the two groups, either in the intention-to-treat analysis (82.8% vs 80.3%, *P*=.74) or in the per-protocol analysis (92.3% vs 90.4%, *P*=.81). Adherence and gastrointestinal side effects were similar between the metronidazole and placebo groups. The microbiologic assessment at 30 days showed decreased recovery of Gardnerella, *Mycoplasma genitalium*, *Atopobium vaginae* and other anaerobic bacteria in those treated with metronidazole. More women treated with metronidazole developed vulvovaginal candidiasis. Clinical cure was similar in both groups (96.7% vs 90.4%, *P=.13*)

Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here.

Does this meet PURL criteria?			
Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	No

Bottom line: Patient-oriented outcomes were not significantly different in women receiving metronidazole compared with placebo, but a reduction in anaerobic bacteria was noted in those treated with metronidazole at 30-day follow-up. This does not require a change in practice with the Centers for Disease Control and Prevention recommending ceftriaxone, doxycycline, and metronidazole for outpatient treatment of PID. The dose of intramuscular ceftriaxone now recommended (500 mg) is higher than what was used in the study (250 mg).

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Can you coadminister the COVID-19 and influenza vaccine?

Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults in the UK (ComFluCOV): a multicentre, randomised, controlled, phase 4 trial

Lazarus R, Baos S, Cappel-Porter H, et al. Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults in the UK (ComFluCOV): a multicentre, randomised, controlled, phase 4 trial. *Lancet*. 2021; 398(10318): 2277-2287. doi:10.1016/S0140-6736(2102329-1)
DOI 10.1097/EBP.0000000000001683

KEY TAKEAWAY: Concomitant administration of six different combinations of COVID-19 and influenza vaccines raised no safety concerns, produced acceptable reactogenicity profiles, and preserved binding antibody responses. The COVID vaccine did not affect the influenza antibody response.

STUDY DESIGN: Randomized controlled phase 4 trial.

LEVEL OF EVIDENCE: Step 2.

BRIEF BACKGROUND INFO: With the COVID-19 pandemic in its third year and the flu season's return, concerns prevail about receiving both vaccines at the same time. Many patients' second dose or booster for COVID-19 may coincide with flu season. Ensuring patients receive the appropriate care and not delay possible lifesaving vaccines is important.

PATIENTS: Adults with COVID vaccination.

INTERVENTION: Combined COVID and influenza vaccines.
CONTROL: Separate COVID and influenza vaccines.
OUTCOME: Systemic reactions.

SECONDARY OUTCOMES: safety and reactogenicity
METHODS BRIEF DESCRIPTION:
- 679 adults across 12 UK hospitals who had received their first dose of a two-dose series COVID vaccine were included.
- At the start of the trial, patients randomly received their second COVID vaccine with the influenza vaccine or with placebo.
- 21 to 28 days after the first visit, the experimental group received a placebo injection and the control group received the influenza vaccine.
- 42 to 56 days after the first visit, patients were assessed for safety, side effects, and immune response.

INTERVENTION (# IN THE GROUP): 340
COMPARISON (# IN THE GROUP): 339

FOLLOW-UP PERIOD: 56 days.

RESULTS: No difference was observed in adverse events whether COVID and influenza vaccines were administered together or separately. The proportion of patients who reported one or more systemic events after receiving either influenza vaccine or saline injection at day 21 was similar.
- ChAdOx1 COVID Vaccine+QIVc ITT Influenza Vaccine: risk difference (RD) –1.3 (95% CI, –14 to 12)
- BNT162b2 COVID Vaccine+QIVc ITT Influenza Vaccine: RD 6 (95% CI, –6 to 19)
- ChAdOx1 COVID Vaccine+aTIV ITT Influenza Vaccine: RD 10 (95% CI, –5 to 26)
- BNT162b2 COVID Vaccine+aTIV ITT Influenza Vaccine: RD –13 (95% CI, –34 to 8)
- ChAdOx1 COVID Vaccine+QIVr ITT Influenza Vaccine: RD 3 (95% CI, –13 to 18)
- BNT162b2 COVID Vaccine+QIVr ITT Influenza Vaccine: RD 7 (95% CI, –12 to 25).

No difference was observed between concurrent or separate vaccine administration in anti-spike immunoglobulins, seroconversion rates, or hemagglutinin.

LIMITATIONS:
- Potential bias with participant-reported primary outcome.

- Influenza vaccine versus sodium chloride potentially unmasked allocation and post hoc analysis suggested more patients guessed their allocation correctly than by chance.
- The cellular quadrivalent influenza vaccine cohorts were added partway through the trial possibly affecting the generalizability of results. EBP

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Is dual antithrombotic therapy associated with better cardiovascular and bleeding outcomes than standard triple antithrombotic therapy in patients with atrial fibrillation after cardiac stenting?

EVIDENCE-BASED ANSWER

Dual antithrombotic therapy consisting of a direct oral anticoagulant and P2Y12 inhibitor is as effective as triple antithrombotic therapy consisting of warfarin plus dual antiplatelet therapy for the prevention of cardiovascular events (SOR: **A**, systematic review of randomized controlled trials [RCTs]) while reducing bleeding events by 41% (SOR: **A**, systematic review of RCTs).

DOI 10.1097/EBP.0000000000001637

A 2018 meta-analysis of two randomized controlled trials (RCTs; N=4,849) examined the safety and efficacy of direct oral anticoagulant (DOAC)-based antithrombotic strategies in adult patients with atrial fibrillation (AF) who underwent percutaneous coronary intervention (PCI).[1] The trials included adults with documented AF requiring anticoagulation therapy undergoing PCI within the previous five days. Intervention groups received DAT consisting of a DOAC (rivaroxaban 15 mg once daily [renally dosed if indicated] or dabigatran 110 or 150 mg twice daily) in combination with a P2Y12 inhibitor (clopidogrel 75 mg once daily, ticagrelor 90 mg twice daily, or prasugrel 10 mg once daily). The control groups received standard TAT with warfarin (titrated to INR 2.0 to 3.0) plus dual antiplatelet therapy (aspirin ≤100 mg daily and a P2Y12 inhibitor). Researchers followed patients for 12 months. The primary efficacy outcome was a composite of cardiovascular events (myocardial infarction, stroke, systemic embolism, death from cardiovascular causes, and unplanned revascularization). The primary safety outcomes were any bleeding that was clinically evaluated and major bleeding, defined by the International Society of Thrombosis and Haemostasis (ISTH) as bleeding resulting in death, symptomatic bleeding into an end organ, or a drop in hemoglobin of 2 g/dL. DAT was not associated with a significant increase in cardiovascular events (relative risk [RR] 1.0; 95% CI, 0.89–1.2), myocardial infarction (RR 1.1; 95% CI, 0.81–1.4), or stent thrombosis (RR 1.5; 95% CI, 0.86–2.5) when compared with TAT. DAT was associated with a decreased risk of all bleeding events (RR 0.66; 95% CI, 0.59–0.75) and major bleeding events (RR 0.59; 95% CI, 0.47–0.73) compared with TAT. Tests for heterogeneity and publication bias were not significant. Limitations include the use of different dosages of DOACs than previously approved for prevention of thromboembolic complications and duplication of the control group in both studies for analysis of two intervention arms.

A 2019 multicenter noninferiority RCT (n=1,506) investigated the safety and efficacy of edoxaban in combination with a P2Y12 inhibitor in patients with nonvalvular atrial fibrillation who underwent PCI.[2] The trial included adults (median age 70 years old) who required anticoagulation for nonvalvular AF and had undergone stent placement within the previous five days. Patients with major comorbidities such as mechanical heart valves, moderate-to-severe mitral stenosis, and end-stage renal disease were excluded. PCI was performed in 52% of patients for acute coronary syndrome and in 48% for stable CAD. The intervention group received DAT with edoxaban 60 mg daily plus the clinician's choice of P2Y12 inhibitor for 12 months, whereas the control group received TAT consisting of warfarin (titrated to INR 2.0–3.0) plus a P2Y12 inhibitor for 12 months and aspirin 100 mg daily for 1 to 12 months (median 66 days). The main efficacy outcome was the composite of cardiovascular death, stroke, systemic embolic events, myocardial infarction, and definite stent thrombosis. The primary safety outcome was a composite of ISTH major and clinically relevant nonmajor bleeding (defined as bleeding not meeting criteria for major bleeding but requiring a hospital admission, a physician-guided treatment, or an interruption or discontinuation of the study drug). The edoxaban-based DAT group was noninferior in preventing the composite cardiovascular outcomes compared with TAT (hazard ratio [HR] 1.1; 95% CI, 0.71–1.7). No difference was observed between the interventions in bleeding event rate (HR 0.83; 95% CI, 0.65–1.1). Limitations of this study include heterogeneity in choice of P2Y12 inhibitor, lack of a placebo for the aspirin component, and lack of blinding

of local investigators (offset by using a team of blinded outcome event adjudicators). EBP

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What is the best treatment for children with ADHD?

EVIDENCE-BASED ANSWER

Multiple medications are effective in treatment of ADHD; of these, amphetamines appear most efficacious (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Combination treatment with behavioral therapy and stimulant pharmacotherapy is consistently more effective than behavioral or stimulant pharmacotherapy alone (SOR: **A**, systematic review of RCTs). Preschool-aged children (4–6 years old) should be initially treated with behavioral therapy alone and methylphenidate may be considered if initial treatment fails (SOR: **C**, clinical practice guideline).

DOI 10.1097/EBP.0000000000001618

A 2018 meta-analysis of 82 double-blinded randomized controlled trials (RCTs; N=14,346) compared the effectiveness of monotherapy with various pharmacological treatments for ADHD in children and adolescents.[1] Both children (5–11 years old) and adolescents (12–17 years old) were identified with ADHD per diagnostic and statistical manual of mental disorders (DSM) III–IV criteria or International Classification of Disease (ICD)-9 and ICD-10 codes. Main medications included were amphetamines (5–40 mg/d), atomoxetine (0.5–1.8 mg/kg/d), bupropion (50–150 mg/d), clonidine (0.2–0.6 mg/d), guanfacine (1–4 mg/d), methylphenidate (18–54 mg/d), and modafinil (200–300 mg/d). All trials lasted at least one week. Treatment efficacy was measured using validated symptom inventories by clinicians and teachers, and tolerability was defined as the proportion of patients who withdrew due to any side effect. Endpoints were calculated using standardized mean differences (SMDs) and odds ratios (ORs). All medications listed above were superior to placebo in clinician-rated efficacy in both children and adolescents (**TABLE**). In head-to-head comparison, efficacies based on clinician ratings were statistically significant favoring amphetamines over atomoxetine (SMD –0.46; 95% CI, –0.65 to –0.27), modafinil (SMD –0.39; 95% CI, –0.67 to –0.12), and methylphenidate (SMD –0.24; 95% CI, –0.44 to –0.05) in children and adolescents. Amphetamines (OR 2.3; 95% CI, 1.4–3.9) and guanfacine (OR 2.6; 95% CI, 1.2–5.8) showed inferior tolerability versus placebo in both children and adolescents.

A 2017 systematic review and meta-analysis of 190 RCTs (N=26,114) compared the safety and efficacy of pharmacological and nonpharmacological ADHD treatments in children and adolescents.[2] All patients were under the age of 18 years old, diagnosed with ADHD, and were treated for at least three weeks. Comparisons included pharmacological (such as amphetamines and atomoxetine), psychological (such as parent training), complementary and alternative medicine (such as polyunsaturated fatty acids), and combined interventions against each other or against placebo or control. Treatment response was defined as the proportion of patients who displayed symptom improvement on standardized rating scales. After pooling of trials, behavioral therapy (15 trials, N=1,106), stimulant medication (53 trials, N=5,831), and nonstimulant medication (40 trials, N=4,741) all showed statistically superior efficacy as monotherapies versus placebo. Complementary and alternative medicine treatments (10 trials, N=519) failed to show superior efficacy compared with placebo. Stimulant monotherapy was superior to behavioral therapy alone (OR 2.1; 95% CI, 1.1–4.0) and nonstimulant monotherapy (OR 1.6; 95% CI, 1.2–2.0). Combination of behavioral therapy and stimulants was superior to stimulant monotherapy (OR 2.2; 95% CI, 1.1–4.3), nonstimulant monotherapy (OR 3.4; 95% CI, 1.7–7.1), and behavioral monotherapy (OR 4.6; 95% CI, 2.5–8.8).

TABLE. Mean change in ADHD symptoms with various medical therapies as rated by clinicians[1]

	Treatment efficacy		
	No. of RCTs	Standardized mean difference	95% CI
Amphetamines	6	–1.02	–1.19 to –0.85
Atomoxetine	21	–0.56	–0.66 to –0.45
Bupropion	1	–0.96	–1.69 to –0.22
Clonidine	1	–0.71	–1.17 to –0.24
Guanfacine	7	–0.67	–0.85 to –0.50
Methylphenidate	9	–0.78	–0.93 to –0.62
Modafinil	5	–0.62	–0.84 to –0.41

A 2019 evidence-based guideline from the American Academy of Pediatrics gave several recommendations for ADHD treatment in children and in adolescents that varied based on patient's age.[3] For preschool-aged children (4–6 years old), Parent Training in Behavior Management was recommended (grade A; high-quality evidence), with methylphenidate to only be considered if behavioral interventions did not provide improvement (grade B; moderate-quality evidence). For children 6 to 12 years old, any Food and Drug Administration–approved ADHD medication and Parent Training and behavioral classroom interventions were recommended (Grade A; high-quality evidence). EBP

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Does a history of AKI increase the risk of developing AKI in the future during strenuous activity?

EVIDENCE-BASED ANSWER

Prior acute kidney injury (AKI) during strenuous activity probably does not increase the risk of developing a subsequent AKI during strenuous activity. Healthy subjects have smaller changes in estimated glomerular filtration rate preexercise and postexercise over time when successive sessions of activity are in close proximity (within days; SOR: **C**, small observational studies reporting disease-oriented evidence).

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A 2019 prospective observational cohort study in 20 male volunteers in the UK military (average age 25 years old) compared serum creatinine (sCr) at rest and at eight minutes after bouts of 60 minutes of standardized

exercise performed at baseline in the UK and then at days 2, 6, 9, and 23 in a heat acclimatization chamber in Cyprus.[1] The primary outcome of acute kidney injury (AKI), defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria (sCr rise ≥26.5 μmol/L) or the risk, injury, failure, loss, end-stage (RIFLE) criteria (fall in estimated glomerular filtration rate [eGFR] >25%), occurred after 26 of 100 exercise exposures. A total of 14 cases of AKI occurred at baseline and only one case by day 23. No difference was observed in resting sCr at baseline versus day 23; however, a smaller increase in sCr was observed on day 23 compared with baseline in preexercise versus postexercise (baseline delta change=35 μmol/L, day 23 delta change=9 μmol/L, P=.0154). The decrease in postexercise eGFR was also smaller by day 23 (31.4% delta at baseline, 11.9% delta on day 23, P<.0001), suggesting that changes in eGFR become less pronounced after adaptation to repeated bouts of strenuous exercise. Limitations included a small number of participants who were all young, male, and generally healthy.

A 2016 retrospective observational study evaluated sCr levels in 627 blood samples collected within a few minutes after completion of the 2011, 2012, and 2014 161-km Western States Endurance Run.[2] The RIFLE criteria were used to define risk of AKI (1.5× increase in sCr) and AKI (2× increase in sCr). Postexercise sCr was compared with calculated expected baseline sCr based on age (using eGRF or 100 cc/min for age <40 years old and 140 cc/min minus age for >40 years old). A total of 36% (n=227) of samples met risk and 4.9% (n=31) met AKI criterions. No correlation was observed with age, sex, running experience, or recent training. Of 38 finishers with at least two races with known sCr levels, 42% (n=16) met risk and 5.3% (n=2) met AKI criterion after the first race and 47% (n=18) met risk and 7.9% (n=3) met AKI after the second race. The incidence of risk or injury among these 38 finishers was similar to the 36% when examining all 627 finishes. Among the 16 athletes who met risk criteria in the first race, 75% (n=12) again met risk/ AKI criterion in a subsequent race, which was greater than the rate of 36% (n=277) of athletes meeting risk/AKI criterion among the total study population (P=.0026). This was also higher than the subset of 38 athletes with postrace sCr available for multiple races (47%, n=18, P=.038). In the 16 individuals meeting risk/AKI criterion, no difference was observed in sCr compared with a subsequent race (P>.3). In addition, the majority (56%) of these individuals had a smaller change in eGFR after the second race compared with the first. Limitations included the retrospective observational nature of the study, and that it was performed in a generally fit population. In addition, assumption of baseline sCr extrapolated with an unvalidated age-based equation could not accurately estimate post-race change from baseline.

A prospective observational study in 2014 (n=30) compared GFR and sCr from blood drawn before and immediately after stages at mile 25 (n=29), 75 (n=15), and 140 (n=14) during the Gobi 2008 (n=10), Sahara 2008 (n=7), and Namibia 2009 (n=13) seven-day, six-stage 150-mile RacingThePlanet ultramarathon running series.[3] RIFLE criteria were used to define risk of AKI and AKI. GFR (mg/dL) was reduced at the finish of each of the three assessed stages individually compared with baseline (baseline: 103±21.6; stage 1: 75±18.6; stage 3: 73±17.7; stage 5: 72±19.7; P<.001 for all); however, no difference was noted in baseline GFR or GFR change among stages. Moreover, sCr and GFR returned to baseline levels before the start of the subsequent stage. Most participants had some form of renal impairment (risk and injury, respectively: stage 1, 45% and 10%; stage 3, 67% and 13%; stage 5, 57% and 7%) but the rate did not increase as the stages progressed. Limitations included a small study population, pooling of data between multiple races, and a lack of control for NSAID use, caloric intake, actual fluid ingestion, and ambient temperature. EBP

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Do Omega-3 fatty acids slow memory loss in patients with cognitive impairment or dementia?

EVIDENCE-BASED ANSWER

Omega-3 fatty acids do not slow memory loss in patients with dementia (SOR: **A**, meta-analysis of 3 good-quality randomized controlled trials [RCTs]) nor do they appear to improve cognition in those with non–dementia-related cognitive impairment (SOR: **B**, 2 low-quality RCTs).

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A 2016 meta-analysis of three randomized controlled trials (RCTs; N=632) compared the efficacy and safety of omega-3 fatty acid supplementation with placebo over six months for people with mild-to-moderate DSM-IV diagnosed Alzheimer disease (AD).[1] Patients were 53% female, mean age in mid-70s, and well-nourished. Outpatients naive to omega-3 supplementation were randomized to omega-3 polyunsaturated fatty acid (PUFA) supplements consisting of 0, 600, or 975 mg/d eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) between 1,750 and 2,300 mg/d or a placebo pill. Compliance was confirmed by significant elevations in treatment serum fatty acid levels. Cognition and function levels were measured using a validated AD assessment tool and were pooled and converted into standardized mean differences (SMDs). After pooling of all three trials, patients treated with omega-3 PUFAs for six months had no improvement in cognition when compared with placebo (SMD –0.02; 95% CI, –0.19 to 0.15). Adverse events were inconsistently reported in two studies, and in one trial (n=402) comparing 900 to 1,100 mg of DHA daily with placebo, no difference was noted in the combined outcome of death, hospitalization, and life-threatening incidents (relative risk 1.1; 95% CI, 0.78–1.4). Limitations included short follow-up periods, cognition assessment tools with limited sensitivity of measuring change, and a per-protocol analysis.

A 2014 RCT (n=199) compared the effect of 180 mg of DHA plus 120 mg of EPA with placebo capsules on cognitive performance in the elderly. Patients (mean age 75 years old) were recruited from a low-income elderly center in Iran with either normal cognition (n=57) or mild (n=83) and moderate (n=59) cognitive impairment without dementia.[2] Those with a Mini-Mental State Exam (MMSE) score of <10, clinical dementia, or diagnosed with Parkinson disease were excluded. The primary outcome was decrease in cognition from baseline measured by the MMSE and Abbreviated Mental Test (AMT). The AMT measures cognitive impairment on a 0 to 10 scale reported as the average of two tests measured seven days apart. At six months, no difference was noted from baseline in mean MMSE scores between the omega-3 group compared with the placebo group for those with mild (mean difference [MD] –0.19 vs –0.22, *P*=.81) or moderate (MD –0.14 vs –0.28, *P*=.32) impairment. No difference was also noted in AMT scores.

A 2015 RCT (n=76) assessed the benefits of DHA and EPA supplementation to placebo on cognition and mood in individuals with cognitive impairment.[3] Cognitively impaired patients without dementia (n=57) were recruited from the community with reported (self or informant) cognitive changes, showed cognitive decline on testing without meeting the diagnostic criteria for dementia, and were functioning independently. AD patients (n=19) were recruited from memory clinics, were on at least three months stable cholinesterase inhibitor dose, and had MMSE scores in mild range (16–30). Patients (mean age 71 years old) were randomized to two capsules containing omega-3 PUFA supplements (600 mg EPA and 625 mg DHA) or two capsules of olive oil daily. Compliance (fasting lipids and pill counts) and outcomes were measured at one and four months. Primary outcome measures included two variations of the MMSE, one with serial sevens (MMSE-7) and the other with spelling world backwards (MMSE-WB) and four other cognitive assessment scales. After four months, no difference was noted between neither the MMSE-7 (24 vs 23, *P*=.71) nor the MMSE-WB scores (25 vs 23, *P*=.58) when comparing omega-3 fatty acid with placebo. No differences were found in delayed, immediate, or recognition verbal memory and mood. EBP

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In adults with depression, does couple therapy result in better outcomes than individual therapy?

EVIDENCE-BASED ANSWER

In adults with depression, couple therapy and individual therapy have similar effect on depressive symptoms (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Couple therapy also seems to moderately improve relationship distress between partners and patients (SOR: **B**, systematic review of small-sized RCTs with high heterogeneity). A 2019 clinical guideline from the American Psychological Association conditionally recommends problem-focused couples therapy for adults with depression who also have relationship distress if other recommended therapies are not available or acceptable (SOR: **C**, consensus guideline).

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A 2018 systematic review of 13 randomized controlled trials and one quasi-randomized trial (N=651) examined the effects of couple therapy compared with individual psychotherapy, drug therapy, or no treatment of depression. Patients were from Europe, North America, and Israel; they were 80% Caucasian and had moderate depression on average. Mean ages ranged from 34 to 48 years old, aside from one study with a mean age of 68 years old. Participants were heterosexual couples, with a partner diagnosed with depression by DSM-III or DSM-IV criteria. Studies were excluded if they used family therapy, targeted postnatal depression, or had no validated diagnosis or validated scale for depressive symptoms. Participants received 5 to 20 couple or individual counseling sessions. The primary outcomes were depressive symptom level and depression persistence, measured with self-rated questionnaires, including the Beck Depression Inventory, Hamilton Rating Scales, and Inventory of Depressive Symptomatology. The secondary outcome was relationship distress level, measured with the Dyadic Adjustment Scale, Locke-Wallace Marital Adjustment Scale, Maudsley Marital Questionnaire, and Quality of Marriage Index. Follow-up periods for all studies ranged from 3 to 24 months. The review showed no statistical difference between couple therapy and individual therapy in depressive symptom level (nine studies, N=304, SMD −0.17; 95% CI, −0.44 to 0.10) and depression persistence at the end of treatment with varied follow-up periods (six studies, N=237, RR 0.94; 95% CI, 0.72–1.22). The similarity remained in studies that had six-month and 12- to 15-month follow-up periods. Regarding the secondary outcome of relationship distress, couple therapy seemed to be moderately more effective than individual therapy (six studies, N=187, SMD −0.50; 95% CI, −0.97 to −0.02, I^2=59%). The major limitations of these studies were the high heterogeneity, underpowered studies, and multiple biases, such as assessment, performance, and investigator allegiance biases.

The American Psychological Association published a clinical practice guideline for the treatment of depression in 2019. A panel of experts from a variety of backgrounds, including psychiatry, psychology, general medicine, and patients, examined the body of evidence for pharmacological and psychotherapeutic treatments for depression. The guideline was largely based on 10 systematic reviews and meta-analyses published within the past five years at the time the panel made its recommendations. Expert opinion and customer reviews were also used in some areas of the guideline where data were lacking. For initial treatment of depression for general adults, the guideline recommended either second-generation antidepressant or

psychotherapy. The guideline did not recommend a specific type of psychotherapy and noted benefits from behavioral therapy, cognitive, cognitive-behavioral, mindfulness-based cognitive therapy, interpersonal psychotherapy, psychodynamic therapies, and supportive therapy. However, for patients also having relationship distress, the guideline conditionally recommended problem-focused couples therapy if the recommended treatment was not available or acceptable. Multiple limitations were observed for this clinical practice guideline including that the studies focused mainly on individuals with comorbid conditions and in outpatient settings. Also, the populations studied lacked diversity in ethnic and racial backgrounds, gender identity, and socioeconomic status. EBP

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Is there an increased risk of cancer in adult patients taking ARB medications compared with adults who take ACE-I medications or placebo?

EVIDENCE-BASED ANSWER

ACE inhibitors or angiotensin II receptor blockers as a class are not associated with an increased risk of cancer incidence (SOR: **B**, based on 2 meta-analyses, mixed quality studies, and limited evidence).

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A 2016 meta-analysis of 19 randomized control trials (RCTs; N=148,334) assessed the risk of cancer in patients taking angiotensin II receptor blocker (ARB) and ACE inhibitor (ACE-I) medications compared with placebo.[1] The trials included adult patients (mean ages 31.7–69.6 years old, predominantly male, with heterogenous diabetes and smoking incidence). Studies included candesartan, valsartan, irbesartan, telmisartan, and losartan. Most of the control groups were treated with placebo; however, some studies used captopril or ramipril. No dose ranges were listed. The primary outcome was the incidence of cancer and evaluated with intention-to-treat analyses. The average study duration was 3.7 years. Compared with placebo, ARB therapy was not associated with an increase in cancer incidence (7 trials, N=29,214, relative risk [RR] 1.1; 95% CI, 1.0–1.2). ARB use was not associated with an excess risk of cancer compared with ACE-I use (4 trials, N=34,462; RR 1.0; 95% CI, 0.94–1.1). The risk of cancer was not significantly different between ARB plus ACE-I and placebo plus ACE-I (6 trials, N=55,391; RR 0.97; 95% CI, 0.9–1.0), or ARB plus ACE-I compared with ACE-I alone (4 trials, N=34,277; RR 0.99; 95% CI, 0.8–1.2). The authors concluded that ARB medications were not associated with an increase in cancer despite having their most clinically relevant outcome (ARB vs placebo) with the lower end of the CI touching 1. The major limitations of this study included short study duration, heterogenous study populations, and analysis from the pooled drug class (ARB) and not individual medications.

A 2008 meta-analysis of 27 RCTs (N=126,137) evaluated cancer incidence in patients taking antihypertensives.[2] The trials included adult patients treated for hypertension (8 trials), chronic kidney disease (2 trials), coronary artery disease (2 trials), heart failure (3 trials), and myocardial infarction (1 trial) with hypertensive medications (ACE-I, ARB, calcium channel blocker, diuretics, or beta blocker). No other patient-specific inclusion or exclusion criteria were provided. Medication dosing was not provided. The average duration of the studies was 3.3 years. The primary outcome was

incidence of cancer for each of the studied medications. The incidence of cancer in patients using ACE-I or ARB did not differ compared with placebo and no treatment arms (ACE-I with 5 trials, N=7,955; odds ratio [OR] 0.83; 95% CI, 0.6–1.1; ARB with 3 trials, N=9,890; OR 1.1; 95% CI, 0.9–1.1). Limitations included potential heterogenous study populations, short study durations, and data pooled on drug classes (ACE-I/ARB) and not specific medications. EBP

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Does gabapentin decrease alcohol use in patients with alcohol use disorder?

EVIDENCE-BASED ANSWER

Gabapentin for the treatment of alcohol use disorder in adults decreases the number of heavy drinking days compared with placebo by 18% (SOR: **B**, meta-analysis of randomized controlled trials [RCTs] and subsequent small RCT). Effectiveness of gabapentin at increasing abstinence from alcohol remains unclear.

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A 2019 meta-analysis of seven randomized controlled trials (RCTs; N=730) evaluated alcohol-related outcomes after treatment with gabapentin versus placebo in adult patients diagnosed with Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV alcohol dependence or DSM-5 alcohol use disorder.[1] Seventy-two percent of patients were male and 61% white. Specific ages were not reported but all patients were >18 years old. All studies were in the outpatient setting. Gabapentin doses ranged from 300 to 3,600 mg daily. Trial duration ranged from 3 to 26 weeks. The meta-analysis studied gabapentin's effects on six alcohol-related measures (complete abstinence, relapse to heavy drinking, percentage of days abstinent, percentage of heavy drinking days, drinks per day, and gamma-glutamyl transferase concentration). Heavy drinking days were variably described by the included studies as: four drinks per day or 40 g/d for women and five drinks per day or 60 g/d for men, days with measured blood alcohol level >0.08%, or greater than five drinks per day regardless of gender. The authors used risk ratio for the two binary outcomes (complete abstinence and relapse to heavy drinking), and Hedges' g as a measurement of efficacy for the four continuous outcomes. Of these six measures, the effect of gabapentin was found to be significant only on percentage of heavy drinking days (7 studies, N=730, Hedges' g –0.64; 95% CI, –1.22 to –0.06), with values around 0.6 indicating a medium clinical effect. No serious adverse effects of gabapentin were identified among the seven trials analyzed.

A 2020 RCT (n=90), not included in the above meta-analysis, studied the effect of gabapentin versus placebo for outpatient treatment of alcohol use disorder in patients with alcohol withdrawal symptoms.[2] The patients were medically stable adults 18 to 70 years old (average 49.6), 77% male and 95% white. They were required to have a diagnosis of alcohol use disorder (as defined by DSM-5), have had at least five drinks per day in the last 90 days, and to have abstained from alcohol three days before randomization into the trial. Patients were excluded from the trial if they had a history of posttraumatic stress disorder or alcohol withdrawal seizure; met criteria for major depressive disorder, bipolar disorder, psychotic disorder, or eating disorder at time of randomization; were currently pregnant or breastfeeding; or were in withdrawal at time of randomization. Treatment dosing of gabapentin was 300 mg in the morning and afternoon and 600 mg in the evening for a total daily dose of 1,200 mg. Patients in the control group received identical placebo capsules. The trial lasted 16 weeks. The primary outcome was the percentage of patients with no heavy drinking days (defined as 4 or more drinks per day for women or 5 or more drinks per day for men), and the secondary outcome was the percentage of participants with total abstinence from alcohol (no drinking days). Outcomes

were assessed by verbal report and confirmed by percentage of disialo-carbohydrate-deficient transferrin, with a value >1.7% being close to 100% specific for sustained heavy drinking. Gabapentin was superior to placebo in the percent of patients having no heavy drinking days (27% vs 9%; mean difference [MD] 18.6%; 95% CI, 3.1–34.1; number needed to treat [NNT]=5.4) and no drinking days (18% vs 4%; MD 13.8%; 95% CI, 1.0–26.7; NNT=6.2). EBP

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For healthy full-term neonates, does bed-sharing versus no bed-sharing decrease the incidence of SIDS?

EVIDENCED-BASED ANSWER

It depends. A 2-fold increased risk of SIDS was observed in infants who bed-share. However, SIDS is not increased with bed-sharing if the mom is a nonsmoker and the baby is older than 12 weeks old, and SIDS is inconsistently increased when bed-sharing is routine. (SOR: **B**, 2 meta-analysis of case–control studies)

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A 2014 systematic review of 21 case–control and cross-sectional studies looked at bed-sharing, SIDS within the first year of life, and the proportion of infants breastfeeding by 6 months old. Studies were conducted in the United States, Scotland, United Kingdom, New Zealand, and Europe. Participants included male and female infants enrolled in the neonatal period and their mothers and followed up to 2 years. Thirteen case–control studies looked at SIDS and bed-sharing; one case–control and seven cross-sectional studies looked at breastfeeding and bed-sharing. Primary outcomes were the proportion of infants dying of SIDS in the first year of life, and the proportion of infants breastfeeding at 4 to 6 weeks, 3 to 4 months, and 6 months of life. Data were collected by using mailed questionnaires to the infants' mothers. For SIDS, the analysis included a total of 1,845 cases (SIDS) and 11,227 controls (no SIDS); 21% of all participating mothers reported bed-sharing. The rate of SIDS was 25% for infants who bed-shared compared with 11% for infants who did not bed-share (13 studies, N=13,072; odds ratio [OR] 2.36; 95% CI, 1.97–2.83). This study also looked at the difference between routine bed-sharing and isolated bed-sharing on the "last sleep" and did not find a statistical difference in the risk of SIDS. Infants who bed-shared were more likely to breastfeed at 4 weeks (two studies, N=10,779; 76% vs 50%; OR 3.09; 95% CI, 2.67–3.58). The overall quality of evidence was very low due to observational nature of the studies, a wide age group included, and variable control groups used across the studies (Methods, Supplemental Digital Content 1, http://links.lww.com/FPIN/A11).

A 2012 meta-analysis of 11 case–control studies evaluated the relationship between SIDS risk and bed-sharing.[2] Six case–control studies in this meta-analysis were also included in the above meta-analysis. However, this meta-analysis included the important secondary outcome of maternal smoking. Inclusion criteria were case–control studies that examined bed-sharing (the same sleeping surface) and SIDS, had an adequate definition for SIDS, had autopsies in >95% of cases, a clear description of the process of control selection, and sufficient data to calculate OR and 95% CI. The study population was 2,464 cases (SIDS) with 6,495 controls (no SIDS) throughout the United States, Scotland, United Kingdom, New Zealand, and Europe. Patients were both male and female infants; in three studies, they were <12 weeks old. Additional information included whether parents smoked and if the bed-sharing was routine or just on the last night recorded. Twenty-nine

percent of case patients bed-shared compared with 13% of control patients. Overall, bed-sharing was associated with an increased risk of SIDS (11 studies, N=8,959, OR 2.89; 95% CI, 1.99–4.18). When bed-sharing was not routine and only performed on the "last sleep," the risk of SIDS increased (four studies, total number participants not stated, OR 2.18; 95% CI, 1.45–3.28). SIDS risk was not increased when bed-sharing was routine (two studies, total number participants not stated, OR 1.42; 95% CI, 0.85–2.38). An increased risk of SIDS was observed when there was maternal smoking and bed-sharing (4 studies, total number participants not stated, OR 6.27; 95% CI, 3.94–9.99), but not for nonsmokers (3 studies, total number participants not stated, OR 1.66; 95% CI, 0.91–3.01). Bed-sharing with infants <12 weeks old increased the risk of SIDS (3 studies, total number participants not stated, OR 10.37; 95% CI, 4.44–24.21), but not with infants >12 weeks old (3 studies, total number participants not stated, OR 1.02; 95% CI, 0.49–2.12). A potential limitation of this meta-analysis was that the studies spanned from 1987 to 2006 which was both before and after the "back to sleep" campaign which started in 1994 that decreased the overall rate of SIDS. Another limitation was the diversity in methods across studies, although confounders such as socioeconomic status and sleeping position were controlled. EBP

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Are there effective nonsurgical treatments of bunions?

EVIDENCE-BASED ANSWER

Conservative treatment of bunions (hallux valgus [HV]) with a dynamic stretch HV brace may help reduce pain and is well accepted, but does not deter patients from electing for surgery (SOR: **C**, small randomized controlled trial [RCT]). The use of a custom-mold room temperature vulcanizing silicone toe-separator is a noninvasive addition that might be used to lessen the degree of moderate HV angle but likely has no impact on perceived pain (SOR: **C**, small RCT). Physical therapy combined with a toe separator may improve HV angle, pain, and alignment (SOR: **C**, small RCT).

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A 2019 randomized controlled trial (RCT; n=70) evaluated the effectiveness of wearing a dynamic stretch hallux valgus (HV) brace for at least three months in patients with symptomatic HV considering surgery.[1] Patients were nonobese adults, and those with degenerative changes in the first metatarsophalangeal joint were excluded. Patients were assigned to either the dynamic stretch brace or usual care. All patients agreed to postpone surgery for the duration of the study. Patients were provided clinical and radiologic analyses, along with pain assessment (0–10, higher scores worsening pain) performed at baseline and at least 3 months after initial visit. Radiographic parameters were analyzed by two investigators blinded to each other's assessments. A dropout of 26% in the control and 19% in the dynamic brace group was observed. The difference in change of HV angle between the intervention and control group was the primary outcome as measured by anteroposterior and lateral foot X-rays. No significant difference in HV angle was noted for those in the dynamic brace group compared with the control group (mean difference [MD]

–0.6° vs –0.5°, $P=.8$). However, the brace group did experience significant reductions in pain when walking (MD –0.5 vs 0.8, $P<.05$) and running (MD –1.1 vs 1.0, $P<.01$) compared with the control group. No difference was found in other clinical parameters, but 80% of those in the dynamic brace group indicated they would recommend the treatment to others.

A 2018 RCT (n=90) evaluated the effectiveness of custom-mold room temperature vulcanizing silicone toe-separator (RTVS TS) on HV angle and pain.[2] Adult patients were at least 60 years old with moderate HV angle (20°–40°). Patients with acute inflammation of the first metatarsophalangeal joint, hallux limitus or rigidus, or a history of continuous use of toe separators or HV straps were excluded. Patients were randomized for one year of usual care (proper foot care and appropriate footwear) or usual care plus fitting a RTVS TS and asked to wear it when non–weight-bearing for at least six hours per day. HV angle was evaluated by a radiologist and physiatrist, blinded to the groups, at baseline, 6, and 12 months. Device satisfaction and intent to continue using were measured using a numeric rating scale of 0 (no satisfaction) to 10 (most satisfaction). Weight-bearing anteroposterior radiographs were obtained for evaluation of HV angle and values averaged. Outcome measures were reported using per-protocol analysis. After one year, HV angle decreased in the treatment versus control group significantly (MD –3.3° vs 1.9°, $P<.05$). No difference in pain improvement was noted between the two groups. Device satisfaction and intent to continue use of the RTVS TS were both high in the study group (90%).

A 2018 RCT (n=56) evaluated the effectiveness of wearing a silicone toe separator plus physical therapy in women with symptomatic, moderate HV.[3] Those who already used orthotics and or splints, had previous foot surgery, and had other foot or ankle deformities were excluded. Patients in the treatment group received 12 weeks of physical therapy at three sessions per week and were required to wear the silicone toe separator for at least eight hours per day. Patients in the control group were instructed to avoid surgical and foot orthotic therapy and asked to continue taking anti-inflammatory medications and perform normal activities. Outcomes measured included HV angle, first and second metatarsal angle, and pain on a 0 to 10 visual analogue scale. After one year, HV angle was lower in the treatment versus control group (MD 26 vs 33, $P<.001$), as were the first and second metatarsal angles (MD 12° vs 15°, $P<.001$) and the pain score (MD 2.4 vs 5.9, $P<.001$). EBP

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What are the long-term effects of melatonin on mood and behavior in patients with dementia?

EVIDENCE-BASED ANSWER

In elderly patients with dementia, long-term melatonin (2 weeks or longer) does not improve or worsen mood, agitation, or neuropsychiatric inventory scales (SOR: **A**, consistent results from 2 randomized controlled trials).

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A 2014 multicenter randomized controlled trial (RCT; n=80) evaluated the effects of daily melatonin on function and neuropsychiatric symptoms.[1] Patients were outpatient adults with mild-to-moderate Alzheimer

dementia receiving acetylcholinesterase inhibitors at stable doses two months before recruitment. Participants were a mean age of 75 years old with a qualifying score on a validated mental examination and confirmational head imaging. Those using other pharmacologic sleep agents were excluded. All patients were instructed to spend two hours a day in outdoor light, given placebo for a run-in period, and then randomized to either placebo or melatonin for the active phase. The melatonin group received 2 mg of prolonged release melatonin for 24 weeks while the control group received matching placebo tablets each given nightly 1 to 2 hours before bedtime. Researchers assessed mood and behavioral issues with the Instrumental Activities of Daily Living (IADL) and Neuropsychiatric Inventory (NPI) at baseline and 12-week and 24-week follow-up. The IADL scores range from 0 to 8 with higher scores indicating higher functional ability. The NPI severity scores range from 0 to 36 (12 domains rated 0–3) with higher scores indicating greater symptom severity and are rated by clinicians as well for perceived distress. After 24 weeks, both groups' function improved in comparison with baseline using IADL, but the melatonin group had slightly less improvement in IADL compared with the placebo group (mean difference [MD] 0.77 vs 1.6, $P=.004$). After 24 weeks, melatonin did not significantly affect behavior per NPI severity score (no data given). After 24 weeks, as compared with baseline, melatonin increased perceived caregiver distress using NPI distress scores versus placebo (MD 3.1 vs –0.24, $P=.026$). However, the authors reported this small difference to be clinically irrelevant. Side effects were minimal and differed slightly between the melatonin and placebo group for urinary tract infection (2.6% vs 18%), diarrhea (10% vs 5.9%), and upper respiratory infections (5.1% vs 8.8%).

A 2008 multicenter RCT (n=189) examined the effects of melatonin on emotional and psychological behavior in patients with dementia.[2] Patients (mean age 86 years old) were elderly residents of 12 different Dutch-assisted living facilities, spent most of their time in a common living area supervised by caregivers, and all diagnosed with dementia using DSM-IV criteria. Those who used nonsteroidal inflammatory drugs, had severe kidney dysfunction, or lacked medical data to reach a reliable dementia diagnosis were excluded. Patients were randomized to melatonin at 2.5 mg given 1 hour before bedtime or placebo for a mean of 15 months. Researchers assessed mood and behavior with the Philadelphia Geriatric Center Affect Rating Scale (PGCARS), Multidimensional Observation Scale for Elderly Subjects (MOSES) subscale for withdrawn behavior, and Neuropsychiatric Inventory Questionnaire (NPI-Q) by neuropsychiatric assessments conducted at six weeks before the start of the trial, six weeks after the start of the trial, and then every six months thereafter. PGCARS-positive and PGCARS-negative scores each range from 0 to 15 with higher scores indicating greater positive affect including pleasure, interest, and contentment and negative affect including anger, anxiety, and sadness. MOSES scores range from 0 to 34 with higher scores indicating greater withdrawn behavior. The NPI-Q uses severity scores ranging from 0 to 36 on 12 behavioral items including hallucinations, agitation, depression, anxiety, and appetite disturbances (rated 0 to 3 each) with higher scores indicating increasing severity of symptoms. Melatonin significantly lowered positive affect (MD –0.55; 95% CI, –1.0 to –0.10) and increased negative affect scores (MD 0.82; 95% CI, 0.20–1.4) compared with placebo on the PGCARS. Melatonin also significantly worsened withdrawn behavior on the MOSES compared with placebo (MD 1.0; 95% CI, 0.18–1.9). However, these differences in scores are minimal and of questionable clinical significance. Melatonin did not significantly affect agitation, mood, or neuropsychiatric behavior on the NPI-Q severity scale compared with placebo. EBP

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Are GLP-1 agonists effective for weight loss in obese nondiabetic pediatric patients?

EVIDENCE-BASED ANSWER

In children with obesity, glucagon-like peptide-1 (GLP-1) agonists (specifically liraglutide and exenatide) can reduce body mass index by up to 1.3 kg/m^2 after 20 weeks of treatment (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). This weight loss may not be sustained after discontinuation of therapy (SOR: **B**, single high-quality RCT). Gastrointestinal side effects are common but major adverse effects are rare (SOR: **A**, meta-analysis of RCTs).

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A 2020 meta-analysis of six randomized controlled trials (RCTs; N=368) evaluated the efficacy of glucagon-like peptide-1 (GLP-1) agonists for weight loss among obese children.[1] The trials included patients less than 18 years old (mean age 9.9–15.2 years old) predominantly from Western countries with obesity (defined as body mass index [BMI] ≥95th percentile for age and sex or corresponding to an adult BMI ≥30 kg/m^2 by international standards). One RCT allowed inclusion of children with type 2 diabetes mellitus and prediabetes, whereas the remaining five trials excluded patients with diabetes. The studies also excluded patients with obesity because of genetic conditions or hypothalamic tumor. The interventions were GLP-1 agonists, with three RCTs investigating liraglutide (target dose 3.0 mg daily) and three evaluating exenatide (target dose 0.02 mg daily or 2.0 mg weekly). The authors did not comment on the controls used for the studies. The primary outcome was a change in weight from baseline, with follow-up ranging from 5 to 56 weeks. After 20 weeks of treatment, patients taking GLP-1 agonists had a reduction in body weight of 2.7 kg (6 RCTs, N=368; 95% CI, –3.8 to –1.7) and a reduction of BMI of 1.3 kg/m^2 (4 RCTs, N=328; 95% CI, –1.7 to –0.80) compared with controls. Gastrointestinal symptoms (ie, nausea, vomiting, and diarrhea) were the most common side effects reported, with the majority of symptoms being mild. Liraglutide was associated with an increased incidence of mild or moderate hypoglycemia, but exenatide was not. No episodes of severe hypoglycemia were reported. The authors did not include data quantifying adverse effect incidence. Limitations included short treatment durations, and no investigation of how treatment discontinuation may affect weight long term. In addition, studies that used other weight loss pharmacotherapy in addition to GLP-1 agonists were included and the potential synergistic effects of these medications were not addressed,.

A 2019 multicenter RCT (n=251) evaluated the effect of liraglutide on weight loss.[2] This trial was included in the above meta-analysis but reported findings after treatment discontinuation that were not commented on in the review. Included patients were adolescents (12–17 years old, mean age 14.6 years old, mean BMI 35.6 kg/m^2) with BMI at or above the 95th percentile for age who had poor weight loss response to lifestyle therapy alone, with or without type 2 diabetes mellitus. Researchers excluded patients on medications known to affect weight (except metformin) and those with a history of weight loss surgery. The intervention group received daily liraglutide injections escalated to 3 mg or maximum tolerated dose for 56 weeks, whereas the control group received volume-matched placebo injections. Patients were reassessed at 82 weeks. All patients received counseling on nutrition and physical activity throughout the trial. The primary outcome was the change in BMI standard deviation score (z-score, or the number of standard deviations from the population mean BMI) from baseline. A change in BMI z-score of at least 0.20 was considered clinically significant. Treatment with liraglutide for 56 weeks resulted in a reduction in BMI (z-score difference –0.22; 95% CI, –0.37 to –0.08) with a reduction in body weight of 4.5 kg (95% CI, –7.2 to –1.8) compared with placebo. After treatment discontinuation, the liraglutide group had an increase in the BMI z-score of 0.15 (95% CI, 0.07–0.23) compared with placebo when reassessed at week 82. Adverse effects occurred at similar rates in both groups, but 13 patients in the liraglutide group discontinued treatment because of adverse effects, whereas no patients discontinued treatment in the placebo group. In addition, those treated with liraglutide were more likely to experience gastrointestinal events than the placebo group (64.8% vs 36.5%). Limitations included industry funding, the

inclusion of patients with diabetes, and lack of clear definition of the inclusion criterion: "poor response to lifestyle therapy." EBP

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Is thrombocytopenia a predictor for severe alcohol withdrawal in patients being admitted for alcohol detoxification?

EVIDENCE-BASED ANSWER

Yes, a lower admission platelet count is associated with a more severe alcohol withdrawal syndrome (SOR, **A**: meta-analysis of epidemiologic studies and 2 retrospective case–control studies). Platelet counts below 119,000/mL are associated with higher rates of developing delirium tremens and withdrawal seizures (SOR, **C**: single retrospective case–control study).

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A 2014 meta-analysis of 15 epidemiologic studies (N=3,989) examined predictors of severe alcohol withdrawal symptoms (SAWS) in hospitalized patients undergoing alcohol detoxification.[1] Demographic information of patients was not provided. Patients were hospitalized with alcohol withdrawal as their primary diagnosis. Patients were excluded based on a history of substance use or if their admission to the hospital was due to a diagnosis other than alcohol withdrawal. Because there was no standard definition of SAWS, this study used the presence or absence of delirium tremens (DT) or seizures. Of the 15 studies, five studies directly addressed admission platelet count as a predictor for SAWS of which four studies had adequate reporting of data. At the time of initial evaluation, admission platelet count was significantly lower in patients with DT than their no-DT counterpart (4 studies, N=3,989; mean difference [MD], –45.64/mm^3, 95% CI, –75.95 to –15.33; I^2=76%) and lower in patients with withdrawal seizures than their no-seizure counterparts (2 studies, N=1,160; MD, –59.91/mm^3, 95% CI, –105.69 to 14.13; I^2=78%). The study was limited by heterogeneity between definitions of SAWS (Methods, Supplemental Digital Content 1, http://links.lww.com/FPIN/A8).

A 2019 retrospective case–control study (n=300) evaluated the use of thrombocytopenia in predicting complicated alcohol withdrawal syndrome which was defined as DT or withdrawal seizures.[2] Patients were between 19 and 65 years old (mean age 44 years), and 79% were male. The control group (uncomplicated alcohol withdrawal) was selected to control for age, sex, and length/severity of last binge. A significant difference was observed in the frequency of thrombocytopenia between the complicated alcohol withdrawal group and the non-complicated alcohol withdrawal group (21.3% vs 71.3%, $P<.001$). The risk of complicated withdrawal significantly increased after platelet counts decreased below the cut-off point of 119,000/mL.

A 2015 retrospective case–control study (n=113) examined predictors of the development of DT.[3] Patients had a mean age of 49.5 years old with 94% male in the DT group (n=34) and a mean age of 48.1 years old with 79% male in the non-DT group (n=63). Patients were excluded if they had other possible causes of acute symptomatic seizures such as electrolyte imbalance, hypoglycemia, hyperglycemia, traumatic brain injury, and ischemic or hemorrhagic stroke. Patients in the DT group had a mean platelet count of 68,900/mL lower than the group that did not develop DT (124,800/mL vs 193,500/mL, $P<.001$). The study was limited by small sample size and lack of blinding of investigators. EBP

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Do racial disparities exist in the prescribing and monitoring of opioid medications for chronic noncancer pain?

EVIDENCE-BASED ANSWER

Black and Hispanic patients are less likely than White patients to receive opioid prescriptions for nontraumatic and nonsurgical pain (SOR: **A**, meta-analysis of retrospective observational studies). Compared with White patients, Black patients experience higher rates of opioid dose reduction and discontinuation, increased substance abuse referrals, and reduced pain specialist referrals (SOR: **B**, multiple retrospective cohort studies).

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A 2012 meta-analysis of 34 observational studies (N=393,429) examined the effect of pain type, treatment setting, and study quality on racial and ethnic disparities in prescription pain management, including opioids, in the United States.[1] Most of the studies included African American (79%) or Hispanic patients (59%); a smaller percentage studied Asian/Pacific Island (24%) or American Indian/Alaskan Native patients (9%). Emergency departments were the most common settings. Included studies were largely retrospective observational studies of adults published between 1989 and 2011. Researchers excluded studies done on a single racial group or on minority groups only, those involving "nonanalgesic" pain management, and those involving chest pain as the pain source. The primary outcomes included prescriptions of "any" analgesia, "opioid" analgesia, and "nonopioid" analgesia. Overall, compared with Caucasian patients, both Hispanic patients (11 studies, sample size not available; odds ratio [OR] 0.78; 95% CI, 0.65–0.93; I^2=49%) and African American patients (15 studies, sample size not available; OR 0.70; 95% CI, 0.62–0.80; I^2=53%) were less likely to receive opioid prescriptions for nontraumatic/nonsurgical (ie, chronic noncancer) pain.

A 2019 retrospective cohort study (n=1,097) examined opioid dose reductions by patient demographics and prescribing patterns for long-term opioid therapy (LTOT) within outpatient adult patients of an urban academic medical center.[2] Patients in the cohort had a mean age of 52 years old and included 15% White, 32% Black, 33% Hispanic, and 20% "other" patients. The median baseline dose of opioids for patients was 90 morphine milligram equivalents (MME). Patients with cancer and pain control in acute settings were excluded, as were those with baseline daily opioid dose of <25 MME. The primary outcome was a reduction of daily opioid dose of at least 7.5 MME within two years of the end of baseline study period. Black patients had a higher rate of dose reduction than White patients (50% vs 36%, adjusted odds ratio [aOR] 1.8; 95% CI, 1.2–2.7) when controlling for gender, age, neck pain diagnosis, baseline daily opioid dose, and concurrent benzodiazepine prescription. No significant differences were observed in rate of opioid dose reduction in Hispanic patients compared with White patients (41% vs 36%, aOR 1.2; 95% CI, 0.8–1.8) or in "other" race patients compared with White patients (81% vs 60%, aOR 0.97; 95% CI, 0.6–1.5).

A 2018 retrospective cohort study (n=15,366) evaluated opioid discontinuation patterns after documented illicit drug use by patients.[3] The study was from Veterans Affairs (VA) medical records. Patients were overwhelmingly male (98%) with a mean age of 50 years old at LTOT initiation. Race was limited to Black and White patients. Testing for

illicit drugs was done through urine drug screens. The primary outcome was discontinuation of LTOT after a positive drug test for either cannabis or cocaine. Black patients were more likely than White patients to have opioids discontinued after testing positive for both cannabis (aOR 2.06; 95% CI, 1.0–4.1) or cocaine (aOR 3.3; 95% CI, 1.3–8.5). Additionally, Black patients were more likely to receive a urine drug test in the first six months of LTOT (aOR 1.6; 95% CI, 1.4–1.7).

A 2013 retrospective cohort study (n=1,899) examined racial differences in pain management, including opioid monitoring and follow-up treatment practices.[4] The study included Black (n=253) and White (n=1,646) patients from Pittsburgh VA medical records. Patients >18 years old who filled opioids for 90 days or more were included, while patients with cancer, those who died within 12 months of first prescription, or those using injectable/oral solutions were excluded. The focus was a racial comparison of the following guidelines: use of an opioid treatment agreement, documentation of pain level, urine drug testing, and referral to specialized care. Opioid agreements were completed for 26% of patients, with similar rates for White and Black patients (26.6% vs 24.5%; *P*=.48). Per VA protocols, pain intensity was documented using a 0-to-10 numeric rating scale during primary care visits; this occurred less frequently at primary care appointments for Black patients than White patients (unadjusted beta coefficient –0.12; 95% CI, –0.16 to –0.08). No significant difference was observed in utilization of urine drug screens between White and Black patients (unadjusted OR –1.3; 95% CI, 0.99–1.69); however, Black patients were significantly less likely to be referred to a pain specialist (aAOR 0.62; 95% CI, 0.43–0.90) and twice as likely to be referred for substance abuse than White patients (aOR 2.3; 95% CI, 1.4–3.9). EBP

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Have incidence rates of advanced prostate cancer in African American men changed since the 2012 USPSTF screening recommendations?

EVIDENCE-BASED ANSWER

From 2011 to 2017, all prostate cancer incidence rates in African Americans declined from 211 to 165 cases per 100,000 men; however, the rate of advanced prostate cancer increased from 14 to 16 cases per 100,000 men (No SOR needed; national registry). African Americans were 50% more likely than Caucasians to be diagnosed with advanced prostate cancer on biopsies after 2012 versus before 2012 (No SOR needed; single institution retrospective cohort).

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The Centers for Disease Control and Prevention's National Program of Cancer Registries and National Cancer Institute's Surveillance, Epidemiology, and End Results program continue to monitor cancer diagnoses and rates in the United States.[1] Data from 45 states were collected using the disease classification and coding from the time of diagnosis. Patients were excluded from the database if they had an unknown age, sex other than male or female, or if the cancer was only identified through autopsy report or death certificate. The demographics of males with prostate cancer

TABLE. Incidence rates of prostate cancer among African American men in the United States[1]

Year	All prostate cancer		Advanced prostate cancer	
	Cases	Rate per 100,000	Cases	Rate per 100,000
2011	32,597	211	1,805	13.7
2012	29,507	183	1,923	13.9
2013	29,223	175	2,097	14.7
2014	28,716	164	2,181	14.5
2015	30,402	168	2,472	16.0
2016	31,277	167	2,593	16.2
2017	31,796	165	2,715	16.3

was 72% white, 16% African American, and 7% Hispanic. The incidence rate of all prostate cancer cases per 100,000 decreased in African American men from 2011 to 2017 (see **TABLE**), with a steady decline in all prostate cancer cases from 2011 to 2014, then a stabilizing of cases from 2014 to 2017. However, this was primarily driven by a decrease in localized prostate cancer. Concomitantly, a steady increase was noted in the incidence of advanced prostate disease (ie, disease outside the prostate) from 13.7 cases per 100,000 men in 2011 to 16.3 cases per 100,000 men in 2017 (see **TABLE**). The report did not include any calculations of statistical significance. This report was limited by monitoring cases for only a short period after guidelines changed, and it did not account for confounding factors that could have influenced prostate cancer rates.

A 2019 single institution retrospective cohort study (n=1,096 biopsies) compared prostate biopsy results of African Americans and Caucasians from before and after the 2012 United States Preventive Service Task Force (USPSTF) screening recommendations[2]. The median patient age was 65 years old. Biopsies from men who had a first-time prostate biopsy in the five years before, and in the six years after, publication of the 2012 USPSTF guidelines were included, whereas patients were excluded if they had known prostate cancer before biopsy or if no prostate-specific antigen value was recorded. The analysis included 609 biopsies before the 2012 USPSTF guideline changes and 487 biopsies after the guideline changes and relied on the pathological data and diagnosis recorded at the time of the original biopsy. Among African American patients, compared with the pre-2012 group, the post-2012 group was significantly more likely to be diagnosed with any prostate cancer (65% vs 56%, P=.016) and intermediate- to high-risk disease (47% vs 38%, P=.038) than the preguideline group. In Caucasian patients, no significant difference was observed in the detection rates of any prostate cancer between preguideline versus postguideline groups. African Americans in the post-2012 cohort were 50% more likely than Caucasians to be diagnosed with advanced prostate cancer on their first biopsy (15% vs 10%, P=.008). Clinical outcomes such as surgical outcomes or mortality were not reported. Data were not included on how many patients were screened with PSA before and after 2012, what the pool of biopsy results was obtained from, or why patients were selected for prostate biopsy. This report defined intermediate- to high-risk disease based on histopathological features rather than spread of the disease at time of biopsy. EBP

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Does elderberry reduce acute viral respiratory symptoms?

EVIDENCE-BASED ANSWER

Probably. Elderberry reduces viral respiratory symptoms among patients with influenza but not the common cold (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). However, no difference is observed in the average number of days to complete resolution between elderberry and placebo (SOR: **B**, single RCT). Elderberry–echinacea may be non-inferior to oseltamivir for treatment of influenza symptoms (SOR: **B**, single RCT).

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A 2018 meta-analysis of four RCTs (N=180) assessed the effect of Black elderberry (*Sambucus nigra*) versus placebo on upper respiratory symptoms.[1] Patients were 5 to 59 years old and approximately half were females; other demographics were not presented. Patients had been diagnosed with influenza or "common cold". In the intervention group (n=89), the dosages and formulations included syrup (2–4 tablespoons daily of standardized extract of elderberry), capsules (600–900 mg daily), and lozenges 175 mg taken four times daily. The control groups (n=91) were not described. Upper respiratory symptoms (eg, fever, sinus congestion) were self-reported in all trials; three trials used a visual analog scale of 1 to 10, and one trial used the Jackson scale, which differentiated symptoms from the common cold from other causes. Trials controlled for etiology of viral respiratory symptoms and flu vaccination status. Elderberry significantly reduced duration of upper respiratory symptoms from influenza (3 trials, N=151; effect size [ES] 2.074; 95% CI, 1.32–2.82; $P<.001$) but not common cold infections (1 trial, n=29; ES 0.66; 95% CI, –0.096 to 1.42; $P=.087$). No adverse events (including nausea and vomiting) were reported. This study was limited by failure to report justification for sample sizes, lack of clarity whether samples were intention to treat or per protocol and small sample size.

A 2020 RCT (n=87), assessed whether elderberry decreased influenza's duration and severity.[2] Patients were five years old and older, and 56.3% were male. Patients were recruited from an emergency department with a positive polymerase chain reaction test for influenza, <48 hours of influenza symptoms, and stable for outpatient treatment. The active treatment was fruit juice containing 5.7 g of *Sambucus nigra* (black elderberry) per 15 mL dose, whereas the placebo was identical minus the black elderberry. Patients were randomized to receive 15 mL of elderberry extract 2 to 4 times daily for five days (n=43) or placebo (n=44). Patients in both groups were also given the option to use oseltamivir in combination with elderberry (26 elderberry and 17 placebo patients opted to also take oseltamivir). The primary outcome was alleviation of all influenza symptoms to none or mild for at least 21.5 hours. No difference was observed in the average time to resolution (elderberry 5.3 days vs placebo 4.9 days, $P=.57$). No significant differences were observed in adverse events reported between the elderberry and the control groups, and most common adverse events included dry mouth (5.7%), constipation (4.6%), rash (4.6%), and bad taste (3.4%). Limitations included the small sample size, and that despite randomizing, elderberry patients were significantly more likely than placebo patients to have received the flu vaccine (46.5% vs 20.5%, $P<.05$) and take oseltamivir (60.5% vs 38.6%, $P<.05$).

A 2015 RCT (N=473) compared an elderberry- and echinacea-containing drink with oseltamivir for influenza treatment.[3] Patients were 12 to 70 years old and 50% were female; all were White. Patients were recruited from a primary care office after having been diagnosed clinically with influenza with <48 hours of symptoms. Patients with comorbidities (including cardiac, renal, hepatic, respiratory, or immune disease, among others), influenza vaccination in the past year, or antimicrobial usage in the past month were excluded. Patients were randomized to receive either the drink containing *Echinacea purpurea* and elderberry (276.5 mg *Sambucus fructus succus recentis*) for 10 days (n=203) or oseltamivir (75 mg) for five days followed by five days of placebo, with placebos for both the drink and tablets (n=217). Acetaminophen and dextromethorphan were provided as rescue medications for both groups. Patients self-rated symptoms daily for 10 days on a scale of 0 to 3, with 0 being "not

present" and 3 being "severe." The primary endpoint was the proportion of patients recovered (defined as the first day symptoms were rated as absent or mild in the evening) after one, five, and 10 days of treatment, which was 1.5% versus 4.1%; 50.2% versus 48.8%; and 90.1% versus 84.8% in patients treated with the elderberry and echinacea drink versus oseltamivir, respectively. The elderberry and echinacea drink was found to be noninferior to oseltamivir each day of treatment: after day 1 (Mann–Whitney statistic [MWS] 0.489; 98.3% CI, 0.468–0.506), after day five (MWS 0.507; 98.3% CI, 0.449–0.565), and after day 10 (MWS 0.527; 98.3% CI, 0.488–0.565) as well as throughout the treatment course (generalized Wilcoxon test, $P=.507$; 95% CI, 0.487–0.526). The elderberry and echinacea hot drink was found to be significantly superior at day 10 alone. A higher incidence of adverse events was observed in the oseltamivir group, including five times as many reports of nausea and vomiting. Limitations included the exclusion of at-risk patients, possible confounding effect of echinacea, and a conflict of interest because this study was sponsored by the manufacturer of the herbal drink. EBP

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What are the most effective pharmacologic treatments of anxiety disorders in children and adolescents?

EVIDENCE-BASED ANSWER

SSRIs are more effective in treating anxiety symptoms than placebo and buspirone (SOR: **A**, meta-analysis). SSRIs also reduce anxiety symptoms more than serotonin and norepinephrine reuptake inhibitors at 12 weeks in patients with generalized, separation, or social anxiety disorders (SOR: **A**, meta-analysis). High-dose SSRIs are effective after two weeks, whereas low-dose SSRIs are effective after eight weeks in patients with generalized, separation, or social anxiety disorders (SOR: **A**, meta-analysis).

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A 2019 meta-analysis (22 randomized controlled trials [RCTs], N=2,623) looked at the efficacy and tolerability of pharmacotherapy for pediatric anxiety disorders.[1] Patients had a mean age of 12 years old (range 5–17 years old) diagnosed with anxiety using a validated tool (undefined). Patients were randomized to receive an SSRI (fluoxetine, fluvoxamine, sertraline, or paroxetine), serotonin and norepinephrine reuptake inhibitor (SNRI; atomoxetine, venlafaxine, or duloxetine), 5-HT_{1A} agonist (buspirone), alpha-2 agonist (guanfacine), TCA (imipramine or clomipramine), or benzodiazepine (alprazolam or clonidine). Medication dosing was not reported. SSRIs (7 RCTs, N=691; odds ratio [OR] 4.6; 95% CI, 3.1–7.5, I^2=38.6%), SNRIs (5 RCTs, N=990; OR 2.4; 95% CI, 1.7–3.6, I^2=0%), and alpha-2 agonist (1 RCT, n=83; OR 5.6; 95% CI, 1.4–27) all demonstrated a treatment response, measured as an improvement on validated global function scores, compared with placebo, with SSRIs being the most effective. SSRIs also improved anxiety symptoms over baseline using validated anxiety symptom scores compared with placebo (7 RCTs, N=691; OR 5.2; 95% CI, 2.8–8.8), whereas other antidepressants did not. No difference was noted in all-cause discontinuation or treatment of emergent suicidality between medication classes. This analysis was limited by a lack of multi-arm studies that directly compared medication groups. Finally, comorbid mental health conditions could have confounded the results of treatment response and were not reported.

A 2018 meta-analysis (9 RCTs, N=1,673) compared the response of medication dosing for the treatment of anxiety in children.[2] This analysis included nine of the same articles from the previous meta-analysis, which did not address the effect of medication dosing. Patients were 5 to 17 years old (47% female) with an undefined clinical diagnosis of anxiety. Patients were randomized to receive an SSRI (5 RCTs, N=752; sertraline 50–200 mg/d, fluoxetine 20 mg/d, fluvoxamine 40–300 mg/d, or paroxetine 32.6–50 mg/d), an SNRI (4 RCTs, N=1,053; venlafaxine 142–225 mg/d, duloxetine 53.6–120 mg/d, or atomoxetine 1.3–120 mg/d), or placebo. Treatment response was measured using multiple validated clinical anxiety scales. These data were extracted from the RCTs, and the difference in mean improvement was determined for each trial. SSRI medications had a stronger reduction in anxiety symptom severity score compared with SNRI medications at 12 weeks (9 RCTs, N=1,805; standardized mean difference=–0.16; 95% CI, –0.19 to –0.13). Although response over time did not differ between low-dose and high-dose SSRI, statistically significant improvement occurred sooner (week 2) in the high-dose SSRI treatment group versus statistical improvement occurring later (week 8) in low-dose SSRI treatment group. By week 12, both high-dose and low-dose treatment groups had significantly improved symptoms compared with baseline (**TABLE**).

TABLE. Decrease in anxiety symptoms in children and adolescents with high- and low-dose SSRI[2]

	Treatment Response				
			Week 2	Week 8	Week 12
	No. of Trials	No. of Patients	Standardized Mean Difference (*P*-value)		
High-dose SSRI	2	656	–0.09 (<0.01)	–0.24 (<0.01)	–0.30 (<0.01)
Low-dose SSRI	3	96	–0.09 (0.149)	–0.21 (0.03)	–0.26 (0.02)

This study was limited by the heterogeneity in scoring systems used among the included studies. EBP

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