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EVIDENCE-BASED PRACTICE

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FPIN Family Physicians Inquiries Network

FPIN envisions a primary care workforce that thinks critically, communicates expertly, and utilizes the best current evidence to improve the health of patients.

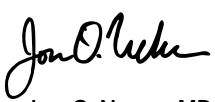
What's in a name

I have delivered somewhere between 500 and 1,000 babies, having lost count years ago. It turns out, all those infants looked pretty much alike. Yes, they all were cute. Yes, they all had a nose like dad and ears like their uncle. Some had a little more hair, others a little less. But let's be honest: put 3 newborns down next to each other and it is pretty easy to get them confused.

Everyone knows this. Entire literary works describe the mischief caused by switching newborns at birth (one usually a prince, the other a peasant). Social order is threatened and many adventures ensue until their true natures are revealed. However, what makes a good fairy tale is not so good in reality, so most hospitals slap a plastic ankle band on infants a few seconds after birth. The infant is then BabyBoy or BabyGirl Jones until the family gets around to assigning a permanent name.

However, if a couple of Baby Joneses or Baby Smiths are at the hospital, the risk of confusion remains, at least among care providers. Researchers decided to see if adding the mother's name to the initial identifier (Marysboy Jones) helped prevent confusion in a neonatal intensive care unit.[1] They used a "retract-and-reorder (RAR) tool," a computer program that tracked when orders were retracted within 10 minutes of placement and reordered on another patient within the subsequent 10 minutes. RAR events were less frequent with the new naming system than with conventional naming (0.038% vs 0.06%; absolute risk reduction 0.022%), reducing such errors by 1 in every 4,500 orders. I'm guessing that, usually, more than 45 orders are placed for neonatal intensive care patients during their hospitalization, so at least 1% of patients benefited.

Now 1% may not sound like a lot, but I like how these authors were thinking. Industrial-scale medicine depersonalizes people and that can be dangerous. We need more good ideas like this to assure that we are treated as individuals when hospitalized and that all our small princes and princesses make it safely to their proper homes.



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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.

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What are the risks associated with hormone therapy in transgender patients?

EVIDENCE-BASED ANSWER

All-cause mortality is higher in male-to-female (MtF) transgender patients on hormone therapy than untreated males. It is unclear if this difference is due to the hormonal therapy or other factors (HIV/AIDS, illicit drug use, suicide). Hormone therapy for MtF patients is associated with an increased risk of thromboembolic disease, cholelithiasis, hyperprolactinemia, transaminitis, and triglyceride elevations.

Masculinizing hormones in female-to-male (FtM) transgender patients are not associated with increased mortality, myocardial infarction (MI), hypertension, or venous thromboembolism (VTE), but are associated with minimal changes in high-density lipoprotein (HDL) cholesterol and systolic blood pressure (BP) (SOR: **B**, 2 cohort studies and meta-analysis of cohort studies).

Evidence summary

A 1997 retrospective cohort study in the Netherlands investigated morbidity and mortality associated with hormone therapy taken for 2 months to 41 years in 816 MtF (mean age 41) and 293 FtM (mean age 34) persons.[1] Patients were followed for a total of 10,152 patient-years. The MtF group took cyproterone acetate and ethinyl estradiol and the FtM group took testosterone. Each transgender group was compared with an age-adjusted cohort of their biological gender.

No significant difference was noted in all-cause mortality between transgender groups and the general population, but subgroup analysis in MtF patients (aged 25–39) found an increase in all-cause mortality compared with controls (standardized mortality ratio [SMR] 3.9; 95% CI, 2.0–7.0). Subgroup analysis for patients aged 40 to 64 found no difference in all-cause mortality. In the MtF group, there was a higher mortality rate due to suicide (SMR 9.3; 95% CI, 4.9–16) and AIDS (SMR 6.0; 95% CI, 1.2–18) and an increased incidence of VTE (standardized incidence ratio [SIR] 20; 95% CI, 12–26), hyperprolactinemia (SIR 82; 95% CI, 68–99), cholelithiasis (SIR 14; 95% CI, 6.2–28), and transaminitis (SIR 44; 95% CI, 23–78). No significant difference was noted between the FtM cohort and the general female population in the incidence of MI, hypertension, and VTE.[1]

In 2011, a follow-up study published additional mortality data for 966 MtF (mean age 31) and 365 FtM (mean age 26) patients on hormone therapy between 1975 and 2007.[2]

At mean follow-up of 19 years, all-cause mortality was 51% higher in the MtF cohort (SMR 1.5; 95% CI, 1.5–1.6). In the MtF group, mortality was higher from ischemic heart disease (SMR 1.6; 95% CI, 1.4–1.9). Current oral ethinyl estradiol use versus former or never use in the MtF cohort was independently associated with a 3-fold greater risk of death due to MI or stroke (adjusted HR 3.1; 95% CI, 1.3–7.6). Hormone treatment was not associated with increased all-cause mortality in the FtM cohort.[2]

A 2010 meta-analysis of 16 observational studies (including the 1997 cohort study above) included 1,471 MtF and 651 FtM patients (mean age 31) on hormone therapy for at least 3 months and examined the effect on BP, serum lipids, cardiovascular events, and VTE.[3] Hormone regimens included estrogens with occasional adjunctive spironolactone for MtF patients and testosterone with adjunctive progesterone for FtM patients.

Hormone therapy was associated with an increase in fasting serum triglycerides in the MtF cohort (5 studies, n=173; weighted mean difference [WMD] 23 mg/dL; 95% CI, 4.8–42) and in the FtM cohort (4 studies, n=148; WMD 31 mg/dL; 95% CI, 7.5–55). In the FtM group, HDL was decreased (5 studies, n=160; WMD –6.1 mg/dL; 95% CI, –11 to –0.73) and systolic BP was increased (4 studies, n=148; WMD 1.7; 95% CI, 0.21–3.3). Meaningful conclusions about patient-oriented outcomes could not be made because of sparse, poor-quality data and significant heterogeneity across studies.[3] EBP

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Oxybutynin for hyperhidrosis; it's no sweat

Schollhammer M, Brenaut E, Menard-Andivot N, et al. Oxybutynin as a treatment for generalized hyperhidrosis: a randomized, placebo-controlled trial. *Br J Dermatol*. 2015; 173(5):1163–1168.

An RCT of 62 adult patients with hyperhidrosis evaluated the effectiveness of oral oxybutynin on symptom improvement. Patients were started at oxybutynin 2.5 mg and titrated up to 7.5 mg in 1 week or a matching placebo.

The primary outcome was improvement of ≥1 point on the Hyperhidrosis Disease Severity Scale (HDSS), a single question answered by patients rating disease severity on a scale from 1 to 4. In the trial, 83% of patients had generalized hyperhidrosis (defined as ≥2 locations on the body).

In the intention-to-treat analysis, more patients taking oxybutynin achieved the primary outcome compared with placebo at 6 weeks (60% vs 27%; *P*<.01; NNT=3). Dry mouth was the most common adverse effect (43% in the treatment group vs 3% in the placebo group; *P*<.01). However, no patients discontinued the medication due to adverse effects.

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: Oxybutynin is a good option for patients with generalized hyperhidrosis. It is easy to implement into daily practice, but may still be a second- or third-line option depending on patient preference or location of symptoms.

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EVIDENCE-BASED PRACTICE LEARNING OBJECTIVES

1. To become knowledgeable about evidence-based solutions to commonly encountered clinical problems.
2. To understand how ground-breaking research is changing the practice of family medicine.
3. To become conversant with balanced appraisals of drugs that are marketed to physicians and consumers.

Extending letrozole treatment to 10 years may prevent recurrent breast cancer

Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med*. 2016; 375(3):209–219.

This randomized, double-blind, placebo-controlled trial assessed the effect of extending dosing of letrozole from 5 years to 10 years in a group of 1,918 postmenopausal women with breast cancer across North America. This study enrolled participants if they had completed 4.5 to 6 years of aromatase inhibitor therapy (with or without tamoxifen) and were disease free. Further stratification controlled for lymph node staging and adjuvant chemotherapy.

The therapy group received of letrozole 2.5 mg orally with a goal treatment of an additional 5 years. Primary outcomes measured were disease recurrence, 5-year survival, contralateral breast cancer, and adverse events.

Disease recurrence or occurrence of contralateral breast cancer was less common in the letrozole group than in the placebo group (7% vs 10.2%; hazard risk [HR] 0.66; 95% CI, 0.48–0.91). The rate of 5-year disease-free survival was similar in both groups (95% vs 91%; HR for death 0.97; 95% CI, 0.73–1.28).

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	Yes

Bottom line: Extension of letrozole therapy to 10 years reduces disease recurrence and occurrence of contralateral breast cancer, but does not affect overall mortality. EBP

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Are statins associated with bladder symptoms?

CASE

A 65-year-old woman with coronary artery disease (CAD) presented with urinary urgency and frequency. You initially presumed her symptoms were due to infection, but her urinalysis results were negative. With further questioning, you discover that her symptoms began after she started taking atorvastatin. When you stopped the drug, her symptoms resolved. You then tried her on pravastatin and, later, rosuvastatin, but the same symptoms recurred.

Bottom line

Observational studies have shown both improvement and worsening of lower urinary tract symptoms (LUTS) while taking a statin. Long-term statin use may be associated with a delay in LUTS onset, especially in men. Worsening of LUTS may occur shortly after starting a statin, especially in women, and this effect may attenuate over time. However, the only RCT showed no difference in LUTS symptoms after 6 months in men.

Evidence that statins may improve LUTS

A subanalysis conducted in 2011 included 1,346 men and women (age range 30–79) in the Boston Area Community Health (BACH) survey with hyperlipidemia without preexisting urologic disease to evaluate the relationship between statin use and LUTS.[1]

Using multivariate analysis to control for confounders, no association was found between statin use and LUTS in women of any age or in men <60 years. In older men, an inverse association was noted between statin use and voiding (odds ratio [OR] 0.23; 95% CI, 0.08–0.66), storage (OR 0.24; 95% CI, 0.11–0.56), and overall LUTS (OR 0.15; 95% CI, 0.05–0.44).[1]

A Minnesota study of 2,447 adult men (age range 40–79) followed over 13.8 years examined the association between statin use and new-onset LUTS ascertained by questionnaire responses.[2]

An inverse association was noted between statin use and new-onset LUTS (hazard ratio [HR] 0.39; 95% CI, 0.31–0.49) after adjustments for baseline variables. Statin use was associated with a 6.5- to 7-year delay in the new onset of LUTS. However, dropout rates may have biased outcomes toward healthier participants with fewer symptoms. There was no impact on LUTS if the statin was initiated after the symptoms had already developed.[2]

The only double-blind RCT was multinational and included 350 men aged ≥50 years with LUTS symptoms randomized to atorvastatin 80 mg or placebo.[3] Over 26 weeks, no benefit of atorvastatin over placebo appeared on International Prostate Symptom Score (mean –4.2 vs –3.5; *P*=.263) or other parameters.

Evidence that statins may worsen LUTS

A Japanese study of 1.2 million insured adults (average age 52) used sequence symmetry analysis to link storage symptoms, overactive bladder, and neurogenic bladder diagnoses to statin use.[4]

After the initiation of statin prescriptions, LUTS diagnoses increased at 6 and 12 months, with adjusted sequence ratios (ASRs) of 2.00 (95% CI, 1.18–3.50) and 1.58 (95% CI, 1.10–2.28), respectively. Prescriptions for overactive bladder medications also increased at 6 and 12 months versus the same time interval before statin initiation, with ASRs of 1.82 (95% CI, 1.14–2.97) and 1.47 (95% CI, 1.06–2.04), respectively.[4]

Review of the FDA Adverse Event Reporting System with 44,959,104 drug reaction pairs found 2,681,739 reports of LUTS associated with statin use.[5] ORs were 1.16 (95% CI, 1.10–1.23) for voiding symptoms and 1.25 (95% CI, 1.20–1.30) for storage symptoms; more than half of these symptoms were reported within 3 months. No difference was found for sex, and age was not reported.

In a retrospective review in which 815 women aged >40 years (mean age 57) with bladder pain syndrome/interstitial cystitis were compared with 4,075 age-matched controls, higher statin use was documented in women with bladder pain/cystitis (15.2% vs 9.8%; *P*<.001).[6] This association remained significant in multivariate analysis adjusting for multiple chronic diseases such as diabetes, CAD, chronic pelvic pain, depression, panic disorders, migraines, sicca syndrome, endometriosis, and asthma (OR 1.52; 95% CI, 1.19–1.94).

CONTINUED

CASE WRAP-UP

Because her symptoms were bothersome enough, your patient asked about stopping statin therapy. You counseled her about the risk reduction she received from the statins. However, quality of life was more important to her than CAD risk reduction, so she chose to stop statins altogether and use lifestyle adjustments to manage her CAD risk. EBP

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HDAs HELPDESK ANSWERS

How does caffeine affect aerobic endurance?

EVIDENCED-BASED ANSWER

Consumption of caffeine (around 6 mg/kg) an hour before exercise produces small to moderate improvements in endurance, particularly in increasing time to voluntary exhaustion (TVE) and ratings of perceived exertion (SOR: **A**, meta-analyses of RCTs). Caffeine also produces small improvements in muscle strength and endurance (SOR: **B**, meta-analysis of 30 crossover studies and 4 RCTs).

A 2004 meta-analysis of 40 laboratory-based RCTs (N=414) evaluated the performance effects of caffeine compared with placebo for exercise performance protocols based on cycling, swimming, and running.[1] Protocols included endurance testing (22 RCTs), graded exercise testing to exhaustion (6 RCTs), and short-term high-intensity testing (12 RCTs). Participants were young adults (82% males; mean age 27), who had average or better levels of fitness (VO_2 max >45 mL/kg/min) or had previous, but unspecified, training experiences.

Ingestion of 3 to 13 mg/kg caffeine (median 6.0 mg/kg) 30 to 360 minutes before exercise (median 60 minutes) improved performance by 12% (95% CI, 9.1–15). The **TABLE** summarizes the results for each protocol. Caffeine improved endurance protocols the most, particularly tests of TVE, which are applicable to training and conditioning, compared with time-based trials (TT), which are representative of competition-based performance.

A 2005 meta-analysis of 21 laboratory-based, double-blind placebo-controlled studies (N=202) measured the effects of caffeine on ratings of perceived exertion.[2] Perceived exertion scales are graded self-report scales that range from no perceived effort to maximally perceived effort. Young adults (74% men; age range 20–35 years) ingested 4 to 10 mg/kg (mean 6.0 mg/kg) of caffeine 30 to 360 minutes (median 60 minutes) before exercise testing.

Caffeine improved perceived exertion by 5.6% compared with control (standardized mean difference [SMD] 0.47; 95% CI, 0.35–0.59). Caffeine also improved mean power output with an "all-out" cycling effort by 11% (SMD 0.45; 95% CI, 0.25–0.64).[2]

A 2010 meta-analysis of 34 laboratory-based studies (N=726), including 30 crossover trials and 4 RCTs, compared effects of caffeine with placebo on maximal voluntary muscle contraction strength, measured by the one-repetition

TABLE

Estimate effect of pre-exercise caffeine on performance testing protocols[1]

Test protocol	Effect size		
	No. of trials	(SMD)	95% CI
Endurance testing			
TVE	17	0.68	0.53–0.84
TT	5	0.28	0.08–0.47
Combined	22	0.63	0.50–0.77
Graded exercise testing to exhaustion			
Combined	6	0.17	–0.02 to 0.36
Short-term high-intensity testing			
TVE	4	0.54	0.23–0.85
TT	9[a]	0.00	–0.02 to 0.31
Combined	12	0.16	0.01–0.31
Overall	40	0.41	0.31–0.51

SMD=standardized mean difference; TT=time-based trials; TVE=time to voluntary exhaustion.
[a]One study included both TVE and TT outcomes.

maximum, and muscle endurance.[3] Muscular strength and endurance are positively correlated in that at a given submaximal load, a stronger individual will outperform a weaker individual. College-aged adults (83% males) ingested 1 to 9 mg/kg (median 6 mg/kg) caffeine or placebo before performance testing.

Voluntary contraction strength increased approximately 4% in the caffeine group (SMD 0.20; *P*<.001). Knee extensor strength accounted for most of the effect (SMD 0.37 vs 0.06; *P*<.001) for other muscles. Caffeine also produced a modest effect on endurance (SMD 0.28; *P*<.001).[3]

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Does oral progesterone affect sleep behaviors in postmenopausal women?

EVIDENCE-BASED ANSWER

Progesterone inconsistently decreases sleep arousals and increases sleep time in postmenopausal women (SOR: **B**, small, inconsistent RCTs).

A 2008 double-blind RCT studied the effects of estrogen and progesterone on sleep in 33 postmenopausal women, 50 to 65 years old, over 24 weeks.[1] Patients took estrogen 0.625 mg orally (group 1) or placebo (group 2) daily. Twelve weeks into the study, both groups also took oral medroxyprogesterone 5 mg daily until the end of the 24 weeks. Sleep EEGs were recorded at baseline, 12 weeks, and 24 weeks.

No difference was noted in sleep latency between the groups. Both groups noted fewer EEG sleep arousals after the addition of progesterone; group 1 improved from 8.5 arousals per hour to 2.8 arousals per hour (*P*<.01) and group 2 improved from 16.9 arousals per hour to 4.9 arousals per hour (*P*<.03). In group 2, 63% self-reported frequent arousals while taking placebo alone, a percentage that dropped to 41% after beginning progesterone.[1]

A 2011 double-blind RCT of 8 postmenopausal women, 48 to 74 years old, with no history of sleep or vasomotor issues compared oral nonmicronized progesterone 300 mg daily with placebo for 20 days.[2] At the end of the 20 days, patients were evaluated in a sleep lab for 44 hours and underwent EEG recording during 2 sleep cycles. After the first night, sleep was disturbed by insertion of an intravenous catheter that was used to collect hormone levels for 24 hours.

During the first night, no significant differences were noted in sleep architecture between the groups, but during the second night the progesterone group had 53% fewer sleep arousals (*P*=.05), 20% more total sleep time (*P*=.04), and 44% more total slow wave (stage III and IV sleep) activity (*P*=.04), suggesting deeper sleep. The authors reported no raw data.[2]

A 2008 double-blind RCT crossover study of 10 postmenopausal women, 54 to 70 years old, investigated the effect of 300 mg oral progesterone compared with placebo

on sleep for two 21-day periods separated by a 2-week washout.[3] A baseline EEG was obtained at the beginning of the first period after a night of adaptation to laboratory conditions. Patients were randomized to receive either placebo or progesterone first. Data collection included an overnight sleep EEG at the end of each interval when lights were off from 11 p.m. until 7 a.m.

Total sleep time was 407 minutes in the progesterone group versus 386 minutes in the placebo group ($P<.05$), a difference largely due to fewer sleep arousals in the progesterone group. Shifts between wake and sleep were noted during the first half of the night, with 11 shifts in the progesterone group versus 15 with placebo ($P<.05$). Subjective sleep quality, sleep continuity, and number of hot flashes were not significantly changed.[3]

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Does use of return-to-play guidelines for adolescents after a sports-related concussion improve outcomes?

EVIDENCE-BASED ANSWER

Return-to-play guidelines have not been evaluated, but cognitive and physical rest after a concussion are inconsistently associated with improvement in symptoms and cognitive function (SOR: **C**, inconsistent cohort studies). Rest may be associated with increased risk of repeat concussion (SOR: **C**, small subset of cohort study).

A 2014 prospective cohort study of athletes (N=335) 8 to 23 years old examined factors affecting duration of symptoms from sports-related concussions.[1] Patients with a concussion underwent scoring at each clinical visit postconcussion using the Post-Concussion Symptoms Scale, a ranking of 22 symptoms on a 0 to 6 scale, ranging from asymptomatic to severely symptomatic. Time to recovery was compared with several variables including cognitive activity-days, calculated as the product of the cognitive activity level (scale 0=complete cognitive rest, to 4=full cognitive activity) and days between visits. This outcome was divided into quartiles.

Patients in the top quartile of cognitive activity-days took significantly longer to recover than the other 3 quartiles (data presented in graphic format). Cognitive activity-days were independently associated with symptom duration (hazard ratio [HR] 0.9942; 95% CI, 0.9924–0.9960), supporting the position that decreased cognitive activity resulted in a shorter recovery period. Several factors—including sex, age, loss of consciousness, amnesia, and number of previous concussions—were not associated with prolonged symptoms.[1]

A 2009 cohort study of 562 concussed high school and college athletes compared clinical outcomes and repeat concussions in athletes observing a symptom-free waiting period (SFWP) before return to activity versus athletes who did not observe an SFWP.[2] Symptoms, postural stability, and cognitive function were assessed at baseline, immediately after injury, 2 to 3 hours later, and again on several days during the first week postinjury using the Graded Symptom Checklist, Balance Error Scoring System, and Standardized Assessment of Concussion. A neuropsychological test was administered 1 to 2 days and 1 week postinjury. All tests were readministered at 45 or 90 days. Average SFWP was 3.2 days (95% CI, 2.3–4.1).

Rate of repeat concussion in the same sport season (n=24) was higher in SFWP group than the no-SFWP group (6.5% vs 0.90%; $P<.005$). Most of these repeat concussions (79%) occurred within 10 days of the first concussion. No significant differences were noted between groups, with and without a repeat concussion, on test scores at the 45- or 90-day endpoints.[2]

A 2008 retrospective cohort study of 86 student athletes (average age 16 years) assessed the effect of postconcussion activity level on symptoms and neurocognitive function.[3] Outcomes of verbal memory, visual memory, visual motor speed, impulse control, and reaction time were measured using the Immediate Post-concussion and Cognitive Test

(ImPACT) and converted to percentile ranks compared with age- and sex-matched normative data. Level of activity was categorized by an Activity Intensity Scale (AIS) from 0 (no school or exercise) to 4 (school activity and participation in sports).

Athletes with an AIS of 4 had the worst visual memory and reaction times, scoring below the second and first percentile, respectively, compared with approximately the 50th percentile for athletes with an AIS of 2. No significant differences were reported in the components.[3]

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Are exercise prescriptions effective interventions for increasing physical activity?

EVIDENCE-BASED ANSWER

No, exercise prescriptions have no consistent effect on increasing physical activity (SOR: **B**, systematic review of a low-quality RCT and observational studies and meta-analysis of low-quality RCTs).

A 2014 systematic review examined the effectiveness of physical activity prescriptions from medical providers for the primary prevention of chronic illness.[1] An RCT, a prospective cohort trial, and a pre-post study (N=1,375) met inclusion criteria: a population of healthy adults or adults at risk for diabetes or cardiovascular disease; formal exercise prescription written; and clinical effectiveness measured by change in physical activity, fitness, or biometric changes.

In the cohort study, the proportion of patients who reported meeting the activity guidelines of the Centers for Disease Control and Prevention (CDC)—150 minutes per week of at least moderate intensity exercise—increased from 25% to 58% in patients receiving a physical activity prescription and brief counseling and from 17% to 50% in patients receiving a physical activity prescription, counseling, and referral to an undefined community program. Patients receiving usual care had no change after 8 weeks. The review reported the change from baseline in the intervention groups was significant but not the comparison with the usual care group (*P* values not reported). The 2 other studies in the review found no increase in activity after exercise prescription at 6 months and 1 year per patient self-report via survey. The review authors stated that there was insufficient evidence to recommend activity prescriptions due to poor quality of available trials.[1]

In 2011, a systematic review of 8 European RCTs (N=5,190) compared exercise referral schemes (referral to a gym to start exercising independently); exercise referral schemes with behavioral counseling; in-office physician exercise counseling; intense, instructor-led walking or cycling programs; and usual care.[2] Patients were primarily sedentary, middle-aged, white adults with at least 1 cardiovascular risk factor (ie, hypertension, hyperlipidemia, smoking, or overweight).

Over 6 to 12 months, no difference was noted between exercise referral schemes and usual care in the number of patients who self-reported meeting the CDC activity guidelines (4 trials, n=2,033; relative risk [RR] 1.1; 95% CI, 0.99–1.3). Three of the 4 studies pooled for this outcome were rated as moderate risk of bias due to unclear blinding of outcome assessors and handling of missing data.[2]

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Does exercise promote sleep in the elderly?

EVIDENCE-BASED ANSWER

Aerobic exercise and resistance exercise programs lead to small to moderate improvements in sleep quality and decreases in use of pharmacologic sleep aids in middle-aged to elderly patients (SOR: **A**, meta-analysis of RCTs). Tai chi moderately improves sleep quality, latency, duration, and habitual efficiency, and reduces sleep disturbance and daytime dysfunction in the elderly (SOR: **A**, meta-analysis of RCTs). Baduanjin, an exercise similar to tai chi, also improves sleep quality in elderly patients (SOR: **C**, small RCT).

A 2012 meta-analysis of 6 RCTs (N=305) examined effects of an exercise program on sleep quality in a population of 241 women and 64 men with a mean age range of 48 to 72 years.[1] Of the 6 trials, 5 examined aerobic exercise and 1 trial examined resistance exercises. Participants exercised at 60% to 85% of their peak heart rate for 10 to 60 minutes a day, 3 to 5 times weekly for 16 to 52 weeks. Control groups had no treatment or 90 to 120 minutes of weekly health education. One trial had an average age of 51 for women and 49 for men; the other trials were all men and had an age-range average from 61 to 72.

Outcomes were measured using the Pittsburgh Sleep Quality Index (PSQI) score, a self-assessment tool with 7 component scores (sleep quality, latency, duration, efficiency, disturbances, medication, daytime dysfunction) and 1 global score (overall sleep quality) measured from 0 (no sleep difficulties) to 21 (severe sleep difficulties), with scores of more than 5 indicating clinical sleep impairment.[1]

Compared with the control groups, exercise programs resulted in a small to moderate improvement in overall sleep score (standard mean difference [SMD] 0.47; 95% CI, 0.08–0.86). (Note: An SMD of 0.2 is considered small, 0.6 moderate, and 1.2 large.) Component analysis of the PSQI showed a small to moderate improvement in sleep quality with exercise (SMD 0.47; 95% CI, 0.20–0.73), and a small to moderate reduction in use of pharmacological sleep aids (SMD 0.44; 95% CI, 0.14–0.74) compared with control groups.[1]

A 2014 meta-analysis of 5 RCTs (N=470, mean age range 66–75 years) evaluated the effects of tai chi for improving PSQI scores.[2] Tai chi exercise varied between 20 and 60 minutes, 2 to 5 times weekly with a duration between 8 and 24 weeks. The control groups in all but 2 of the trials received either no treatment or maintained their normal activity. One trial gave health education to its control group; whereas another trial had 1 hour of low-impact exercises 3 times weekly for 24 weeks. Three studies reported the data of the 7 components of the PSQI.

Compared with control, tai chi resulted in a moderate to large improvement in the PSQI overall sleep quality (SMD 0.87; 95% CI, 0.49–1.25). Component analysis showed that exercise improved subjective sleep quality (SMD 0.83; 95% CI, 0.57–1.08), sleep latency (SMD 0.75; 95% CI, 0.07–1.42), sleep duration (SMD 0.55; 95% CI, 0.21–0.90), habitual sleep efficiency (SMD 0.49; 95% CI, 0.23–0.74), sleep disturbance (SMD 0.44; 95% CI, 0.19–0.69), and daytime dysfunction (SMD 0.34; 95% CI, 0.09–0.59).[2]

A 2011 longitudinal RCT examined effects of an Eastern exercise program similar to tai chi called Baduanjin on sleep in Taiwan.[3] Depressed patients were excluded. Fifty-six patients (20 men, 36 women, mean age 72 years) were randomized to an exercise or control group. Patients completed a 12-week Baduanjin program for 90 minutes weekly, whereas the control group received no intervention. Outcomes were measured using the PSQI at baseline, 4, 8, and 12 weeks.

Global PSQI score improved with Baduanjin in all 3 time periods compared with baseline and compared with control. At 12 weeks, the PSQI global score in the Baduanjin group improved from 11.93 at baseline to 6.22 ($P<.001$), but in the control group no significant improvement was noted (11.11 at baseline to 10.50; $P=.903$). The between-group difference was reported to be significant ($P<.001$).[3]

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What are the test characteristics of the Waddell incongruency signs for nonorganic back pain?

EVIDENCE-BASED ANSWER

The answer is uncertain. Although not directly evaluated for determining organic from nonorganic back pain, the Waddell signs do not seem to be useful for predicting ability or inability to return to work or success of rehabilitation. Additionally, they are only weakly associated with factors such as physical signs, pain, illness behavior, and psychological comorbidities (SOR: **B**, cohort and cross-sectional studies)

The Waddell signs are superficial tenderness, simulated movements that produce pain, straight leg raise that improves with distraction, regional weakness or sensory changes that deviate from accepted neuroanatomy, and patient overreaction.

A 2000 prospective cohort study of 69 patients with acute, work-related low back pain of less than 3 weeks' duration undergoing physical therapy evaluated the diagnostic and predictive abilities of the Waddell signs and nonorganic symptoms.[1] The 7 nonorganic symptoms consisted of pain in tailbone, numbness in entire leg, pain in entire leg, whole leg giving way, emergency visits due to back pain, episodes with minimal back pain, and treatments making pain worse. The primary outcome measure was the predictive ability of the Waddell signs and nonorganic symptoms on patients' ability to return to work without restriction within 4 weeks of the initial evaluation. Waddell signs were evaluated by a physical therapist at enrollment and nonorganic symptoms were assessed by patient questionnaire.

The presence of 2 or more Waddell signs had a negative likelihood ratio (LR–) for returning to work of 0.75 (95% CI, 0.51–1.1) with a corresponding positive LR (LR+) of 1.9 (95% CI, 0.91–4.1), indicating that the Waddell signs are not useful for determining inability or ability to return to work. The presence of 3 or more nonorganic symptoms had a LR– for returning to work of 0.62 (95% CI, 0.40–0.96) with a corresponding LR+ of 2.6 (95% CI, 1.3–5.4), indicating that the Waddell signs may have marginal utility for determining inability or ability to return to work.[1]

A 1997 prospective cohort study evaluated the presence of Waddell signs for predicting treatment success or failure in 60 patients with low back pain with a mean age of 38.5 years and a mean duration of back pain disability of 18 months.[2] Patients completed a 3-week inpatient functional restoration program that emphasized improving physical abilities as well as self-management of disability through progressive exercise and structured patient education; patients were followed for 1 year.

No significant correlations were found between the Waddell total positive score (1 point for each Waddell sign present) or changes in score and therapeutic success as measured by behavioral outcomes, such as return to work.[2]

In 2012, a cross-sectional study evaluated the correlation of the Waddell signs to 5 domains in 229 patients with chronic low back pain and an average age of 44 years who attended outpatient rehabilitation.[3] The 5 domains were demographics such as age; physical signs and symptoms such as duration of pain and range of motion; pain; illness behavior such as medication usage and taking sick leave; and psychological factors such as depression and somatization.

Spearman correlation coefficients were calculated between the Waddell signs and the 5 domains and the associations were all considered to be weak. The highest Spearman correlation coefficients were for taking sick leave (0.39) and the somatization subscale of the Symptom Checklist-90-Revised (0.44).[3]

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Is human growth hormone effective for treating burns and skin graft donor sites?

EVIDENCE-BASED ANSWER

Yes, recombinant human growth hormone (rHGH) decreases healing time of burn and skin graft donor sites by up to 9 days, shortens hospital stays by 12 days, and does not affect the rate of septicemia or mortality compared with placebo treatments. rHGH increases the risk for hyperglycemia compared with nontreatment (SOR: **B**, meta-analysis of small RCTs).

A 2014 systematic review of 13 RCTs (N=701) evaluated rHGH with comparable interventions on burn healing time, donor-site healing time, overall hospital stay, mortality, and adverse events.[1] Patients included 289 children and 412 adults 1 to 65 years old, mostly males, with more than 40% body surface area full-thickness burns. The dosing regimens of rHGH were varied, with 0.05 mg/kg per day to 0.5 IU/kg per day given via injection once or twice daily for 5 days to 1 year.

Compared with placebo treatments, hormone-treated burn sites in adults (2 RCTs, n=36) healed faster than nontreated sites (mean difference [MD] –9.1 days; 95% CI, –13.8 to –4.4). Donor sites in adults (2 RCTs, n=36) healed an average of 3.2 days faster (95% CI, 1.5–4.8). Donor sites in hormone-treated children also healed faster than in nontreated children (2 RCTs, n=73; MD –1.7 days; 95% CI, –2.53 to –0.87). The overall length of hospital stay in adults (4 RCTs, n=99) decreased in hormone-treated patients compared with nontreated patients (MD –12.6 days; 95% CI, –17.1 to –8.0). Mortality in adults and children (5 RCTs, n=324) was not significantly decreased in hormone-treated patients (RR 0.53; 95% CI, 0.22–1.3). Hyperglycemia was increased in both adults and children treated with rHGH (4 adult RCTs, n=300, and 1 child RCT, n=40; RR 2.7; 95% CI, 1.7–4.2). The risk of septicemia in adults (4 RCTs, n=267) did not differ in hormone-treated patients compared with nontreated patients (RR 0.61; 95% CI, 0.31–1.2).[1]

A 2016 double-blind, placebo-controlled RCT (N=33) of patients with severe burns evaluated sustained-release (SR) rHGH during the rehabilitation phase.[2] This study included 18 patients (17 men, 1 woman) who received 2 mg SR rHGH in weekly injections for 3 months and 15 patients (all men) who received an identical placebo injection. The primary outcomes studied included scar healing, exercise duration and parameters, change in lean body mass, and change in maximum muscle power.

Evaluation of scar thickness via ultrasonography found no difference in thickness between treatment and placebo groups at 4 or 12 weeks. At 12 weeks, rHGH patients had better VO_2 max than placebo patients (30.9 vs 23.5 mL/min•kg; $P<.05$) and greater lean body mass (48.4 vs 44.4 kg; $P<.05$), but no difference was noted in exercise duration or muscle power. No adverse events were reported.[2]

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How safe and effective are aclidinium inhalers for patients with chronic obstructive pulmonary disease (COPD)?

EVIDENCE-BASED ANSWER

In moderate-to-severe COPD, aclidinium modestly improves quality of life and decreases hospital admissions without any serious adverse events (SOR: **A**, meta-analysis of RCTs). Aclidinium also modestly reduces the rate of COPD exacerbations and rescue inhaler use (SOR: **B**, RCT). Aclidinium improves lung function as well as tiotropium without any difference in adverse events (SOR: **B**, RCT).

A 2014 meta-analysis of 12 RCTs involving 9,547 patients with COPD evaluated the efficacy and safety of aclidinium bromide inhaler 400 mcg twice daily compared with placebo over 4 to 52 weeks.[1] Patients had stable moderate-to-severe COPD, defined as a forced expiratory volume in 1 second (FEV1) of 46% to 58% of predicted and no COPD

exacerbations requiring hospitalization in the previous 3 months. Most patients where white men older than 60 with more than a 10 pack-year smoking history. There was no mention of which medication patients were also taking to control their COPD. The primary endpoint was improvement in FEV1.

Compared with placebo, aclidinium increased predose FEV1 by 90 mL (9 trials, n=4,963; 95% CI, 80–100). For secondary endpoints, aclidinium improved quality of life (7 trials, n=4,442) by a decrease of 5.3 points (95% CI –3.2 to –1.5) on the 100-point St. George's Respiratory Questionnaire (SGRQ, higher scores indicate greater COPD severity). This 3-component questionnaire measures quality of life, symptom severity, and degree of limitation of activities, with a mean difference of 4 points being clinically significant. Compared with placebo, aclidinium decreased the risk of hospital admissions for COPD exacerbations (10 trials, n=5,624; odds ratio [OR] 0.64; 95% CI, 0.46–0.88; number needed to treat=77). There was no increase in deaths or serious adverse events with aclidinium versus placebo.[1]

One study included in the meta-analysis reported additional secondary endpoints not discussed above. This 2012, 24-week RCT involving 828 men and women older than 40 years with at least a 10 pack-year smoking history and moderate-to-severe COPD compared twice-daily aclidinium 400 mcg with placebo.[2] Moderate-to-severe COPD was defined as postbronchodilator FEV1/forced vital capacity (FVC) less than 70% and FEV1 less than 80% of predicted.

Aclidinium resulted in a rate of COPD exacerbations of 0.4 per patient per year compared with 0.6 per patient per year with placebo (P<.05) and increased the percentage of days not requiring rescue inhaler use by 11% (P<.001).[2]

A 6-week, double-blind RCT of 414 patients from the meta-analysis above also compared twice-daily aclidinium 400 mcg with tiotropium 18 mcg daily in addition to placebo.[3] Salbutamol was used for symptom control and patients were allowed to continue their stable use of oxygen, theophylline, and inhaled, oral, or parenteral corticosteroids. Patients were older than 40 years with a minimum 10-pack year smoking history and stable, moderate-to-severe COPD. Stability was defined as no respiratory infections in the previous 6 weeks and no hospitalizations for exacerbations in the past 3 months. Moderate-to-severe COPD was defined as FEV1/FVC less than 70% and FEV1 between 30% and 80% of predicted.

Aclidinium was as effective as tiotropium at improving predose FEV1, with increases of 160 and 123 mL, respectively (P<.0001 for both comparisons vs placebo). No difference was noted in the rate of adverse events between the 2 medications.[3] EBP

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GLOSSARY

ARR=absolute risk reduction
CDC=Centers for Disease Control and Prevention
CI=confidence interval
CT=computed tomography
FDA=US Food and Drug Administration
HR=hazard ratio
LOE=level of evidence
MRI=magnetic resonance imaging
NNH=number needed to harm
NNT=number needed to treat
NSAID=nonsteroidal anti-inflammatory drug
OR=odds ratio
RCT=randomized controlled trial
RR=relative risk
SOR=strength of recommendation
SSRI=selective serotonin reuptake inhibitor
WHO=World Health Organization

Are opioid analgesics taken for more than 90 days effective for patients with chronic low back pain (CLBP)?

Bottom line

Opioid analgesics reduce pain more than placebo in patients with CLBP; however, few trials used opioids for more than 90 days and adverse events were more common with opioids (SOR: **B**, meta-analysis of RCTs at risk of bias). Opioids do not reduce pain more than nonopioid analgesics in patients with CLBP or chronic noncancer pain (CNCP) (SOR: **B**, meta-analyses of RCTs at risk of bias). Patients treated with opioids for CLBP and CNCP experience more non-life-threatening adverse events and discontinue therapy due to adverse events more frequently than patients treated with nonopioid analgesics (SOR: **B**, meta-analyses of RCTs at risk of bias).

Evidence summary

A 2014 systematic review and meta-analysis of 15 RCTs (N=5,540) compared flexible dosing of noninjectable opioids (tramadol, buprenorphine, morphine, oxymorphone, tapentadol, oxycodone, and hydromorphone) versus placebo (13 trials), tricyclic antidepressants (nortriptyline, flupirtine; 2 trials), or celecoxib (1 trial) for treating patients with CLBP.[1] Patients were mostly 40 to 50 years, with slightly more women than men who had moderate CLBP or prior low back surgery. They were followed for 4 to 15 weeks with primary outcomes of pain reduction (3 different scales), function (3 different scales), and quality of life (3 different scales); however, only 2 of the RCTs had follow-up beyond 12 weeks.

Opioids reduced pain and improved function more than placebo, but did not improve either outcome compared with tricyclic antidepressants (see **TABLE 1**). Transdermal buprenorphine reduced pain more than placebo, but the observed functional improvement was not statistically significant (see **TABLE 1**). Fewer patients experienced a 30% or greater decrease in pain with tramadol (50 mg QID) compared with celecoxib (200 mg BID) (n=1,583; RR=0.82; 95% CI, 0.76–0.90). Opioid users reported higher rates of non-life-threatening adverse events (see **TABLE 2**). While no evidence was noted of publication bias, there was a high risk of attrition bias due to dropout rates of 21% to 86%.[1]

A 2015 systematic review and meta-analysis of 10 RCTs (N=3,046) compared noninjectable opioids (tramadol and morphine) versus any nonopioid analgesic for treating patients with CNCP.[2] The causes of CNCP included osteoarthritis (4 trials, n=2,739), low back pain (2 trials, n=272; 1 trial was included in the 2014 systematic review), and neuropathic pain (4 trials, n=167). The participants were mostly 47 to 71 years old, predominantly white, with slightly more women than men. Opioid dosing ranged from 15 to 240 mg daily morphine equivalent and the follow-up period was 4 to 12 weeks. Comparison groups included COX-2 inhibitors, flupirtine, nortriptyline, gabapentin, and mexiletine. Primary outcomes were pain rating (3 different scales), change in function (9 different scales), tolerability (dropout due to a non-life-threatening adverse event), and serious adverse events.

TABLE 1

Treatment outcomes in patients with chronic low back pain receiving opioids vs placebo or nonopioid analgesics[1]

Treatment comparison	No. of trials	N	SMD (95% CI)	
			Self-reported pain	Impaired function
Tramadol vs placebo	5	1,378	–0.55 (–0.66 to –0.44)	–0.18 (–0.29 to –0.07)
Transdermal buprenorphine vs placebo	2	653	–2.5 (–2.7 to –2.3)	–0.14 (–0.53 to 0.25)[a]
Opioids[b] vs placebo	6	1,887	–0.43 (–0.52 to –0.33)	–0.26 (–0.37 to –0.15)
Tramadol vs nortriptyline or flupirtine	2	272	0.21 (–0.03 to 0.45)[a]	–0.11 (–0.63 to 0.42)[a]

SMD=standard mean difference. An SMD of 0.2 is considered small, 0.6 moderate, 1.2 large, and 2.0 very large.

[a]Not statistically significant.

[b]Opioids include morphine, oxycodone, hydrocodone, oxymorphone, and tapentadol.

TABLE 2

Increased risks of adverse events with opioids vs placebo in patients with chronic low back pain[1]

Adverse event	No, of trials	N	Risk difference	95% CI
Nausea	10	3,747	10%	7–14
Headaches	10	3,747	3%	1–5
Dizziness	9	3,493	8%	5–11
Constipation	9	3,493	7%	4–11
Somnolence	8	3,257	6%	3–9
Vomiting	7	3,119	7%	4–9
Pruritus	6	2,865	4%	2–5
Dry mouth	6	1,724	6%	2–10
Fatigue	6	1,645	3%	1–5
Increased sweating	4	1,350	4%	2–5
Hot flashes	2	593	3%	0–5[a]
Anorexia	2	386	4%	1–7

[a]Not statistically significant (*P*=.56).

TABLE 3

Treatment outcomes for opioids (tramadol or morphine) vs nonopioid analgesics in treating chronic noncancer pain[2]

			Results			
Outcome	No. of trials	N	Type	Value	95% CI	Interpretation
Pain reduction	8	1,506	SMD	0.03	–0.18 to 0.24	No difference
50% pain reduction	2	308	RD	0.03	–0.30 to 0.35	No difference
Improved function	6	1,198	SMD	0.17	0.02–0.32	Better with nonopioids
Dropout rate due to lack of efficacy	6	2,912	RD	0.00	–0.01 to 0.01	No difference
Dropout rate due to adverse events	8	3,080	RD	0.09	0.06–0.13	Better with nonopioids
Serious adverse events	6	2,728	RD	–0.01	–0.02 to 0.00	No difference

RD=risk difference; SMD=standard mean difference. An SMD of 0.2 is considered small, 0.6 moderate, 1.2 large, and 2.0 very large.

Opioids did not significantly reduce mean pain compared with nonopioid analgesics, while nonopioid analgesics improved function more than opioids (see **TABLE 3**). Opioid users were more likely to discontinue treatment due to adverse events, but no difference was noted in serious adverse event rates (see **TABLE 3**). Only 1 study was considered high quality; 7 were graded as low quality and 2 were graded as moderate quality. Limitations included poor methodology, incomplete data reporting, and statistically significant heterogeneity.[2] EBP

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Vitamin D supplementation and breastfeeding

Hollis BW, Wagner CL, Howard CR, et al. Maternal versus infant vitamin D supplementation during lactation: a randomized controlled trial. *Pediatrics*. 2015; 136(4):625–634.

This randomized trial compared the effects of 3 vitamin D dosing regimens in 334 breastfeeding mother-infant pairs. In group 1, mother and infant both received vitamin D 400 IU (current standard of practice); in group 2, mothers received 2,400 IU and infants received placebo; and in group 3, mothers received 6,400 IU and infants again received placebo.

Primary outcomes were infant vitamin D levels and the incidence of infant vitamin D deficiency, defined as serum levels <50 nmol/L. The group 2 arm was discontinued due to low infant vitamin D levels.

At 7 months, infant vitamin D levels were similar in groups 1 and 3 (109.1 vs 108.5 nmol/L; *P*=.9) and no difference was noted in the number of infants with vitamin D deficiency (4.2% vs 4.3%; *P*=1.0).

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	Yes	Clinically meaningful	No

Bottom line: High-dose maternal vitamin D supplementation in a breastfeeding woman can transfer enough vitamin D to the infant to sustain optimal infant vitamin D levels. Despite demonstrating a potential alternative to a vitamin D replacement regimen, this study does not evaluate the effect of this regimen on the development of rickets.

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Statins for primary prevention of cardiovascular (CV) events

Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016; 374(21):2021–2031.

This RCT compared the effect on CV mortality and morbidity of rosuvastatin 10 mg vs placebo in 12,705 intermediate-risk patients without CV disease. Patients were men ≥55 years and women ≥65 years with 1 CV risk factor. Two primary outcomes were composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke and composite of the above outcomes with resuscitated cardiac arrest, heart failure, or revascularization.

The first primary outcome occurred less in the rosuvastatin group than in the placebo group (3.7% vs 4.8%; HR 0.76; 95% CI, 0.64–0.91). The second primary outcome also occurred less in the rosuvastatin group (4.4% vs 5.7%; HR 0.75; 95% CI, 0.64–0.88).

Subgroup analysis revealed a statistically significant reduction in primary and secondary outcome for white men, but was not powered to detect differences in women or other ethnic subgroups.

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	Yes

Bottom line: This study supports the growing body of evidence for statins in primary prevention of CV events in white men, but provides insufficient evidence for whether this benefit extends to women or ethnically diverse populations. EBP

Review and Summary Author: Nicholas Shungu, MD, UNC Department of Family Medicine, Chapel Hill, NC

Is acupuncture effective for treatment of knee pain due to osteoarthritis?

EVIDENCE-BASED ANSWER

Acupuncture is slightly better than sham acupuncture in decreasing knee pain due to osteoarthritis (OA), but has a much greater effect than usual care consisting of analgesics, education, and advice (SOR: **A**, 2 meta-analyses of RCTs).

A 2013 meta-analysis including 114 RCTs with 9,709 patients (mean age 55 years) compared acupuncture with sham acupuncture, various physical treatments, standard care (analgesics, education, and exercise advice), placebo, and no intervention for the treatment of pain in OA of the knee.[1] Trials assessed pain as a primary or secondary outcome in adults with knee OA. Trial quality was rated as excellent, good, satisfactory, or poor based on an unreported algorithm. Quality of studies varied significantly. Consequently, separate analyses were performed for all studies, regardless of quality, and for 35 higher quality studies rated at least satisfactory (n=3,499). Pain was evaluated using a variety of instruments, so outcomes were reported as standardized mean difference (SMD). An SMD of 0.2 is considered small, 0.6 moderate, and 1.2 large.

Analysis of the higher quality trials revealed a moderate to large reduction in pain due to knee OA with traditional acupuncture compared with standard care (11 trials, n=878; SMD –1.0; 95% CI, –1.4 to –0.61) and even a moderate reduction with sham acupuncture compared with standard care (8 trials, n=685; SMD –0.68; 95% CI, –1.2 to –0.19). Sham acupuncture compared with true acupuncture favored true acupuncture to a small degree (8 trials, n=685; SMD 0.34; 95% CI, 0.03–0.66). Pain relief outcomes were assessed at less than 7 weeks. Major limitations of this analysis were heterogeneity of comparison groups and small sample sizes.

A 2012 meta-analysis of 29 RCTs that included 17,922 patients compared acupuncture versus usual care, placebo, or sham controls, for chronic pain conditions. The trials addressed 1 of 4 pain conditions that were present for at least 4 weeks: back pain or neck pain, shoulder pain, chronic headache, or OA.[2] Nine trials included patients with OA and some were 3-armed studies. Six included a sham acupuncture control group and 8 included a no-acupuncture control group (2 were ancillary care; 4 were usual care; 2 were nonspecific advice). The results were calculated using raw data from the RCTs and reported as SMD due to the trials using different pain scales.

Over 2 to 6 months, acupuncture for OA resulted in moderately better pain relief than no-acupuncture control (6 trials, n=1,968; SMD 0.57; 95% CI, 0.50–0.64) and slightly better pain relief than sham control (5 trials, n=1,487; SMD 0.26; 95% CI, 0.17–0.34). A major limitation in this study was the heterogeneity of the control groups, both for sham acupuncture techniques and for the no-acupuncture controls.[2]

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What are the best treatments for actinic keratosis?

EVIDENCE-BASED ANSWER

For complete clearance of lesions, 5-fluorouracil, diclofenac, imiquimod, and ingenol mebutate are more effective than placebo. Of these agents, 5-fluorouracil is the most effective. For individual lesions, photodynamic therapy is superior to cryotherapy (SOR: **A**, meta-analysis of RCTs, network analysis of RCTs).

A 2012 Cochrane review (83 RCTs) of 10,036 patients with actinic keratosis assessed the effects of 18 topical treatments, 1 oral treatment, 2 mechanical interventions, and 3 chemical interventions including photodynamic therapy for actinic keratosis.[1]

For the primary outcome, complete clearance according to patient assessment, diclofenac in hyaluronic acid, 5-fluorouracil, imiquimod, and ingenol mebutate were superior to placebo (see **TABLE 1**). For individual lesions,

TABLE 1

Treatment effects of topical medications versus placebo on complete clearance of actinic keratosis by patient assessment[1]

Agent	No. of studies	No. of participants	Risk ratio (95% CI)
3% Diclofenac in 2.5% hyaluronic acid	3	420	2.5 (1.7–3.7)
0.5% 5-Fluorouracil	3	522	8.9 (3.7–21)
5% Imiquimod	9	1,871	7.7 (4.6–13)
0.025% to 0.05% Ingenol mebutate	2	456	4.5 (2.6–7.7)

TABLE 2

Treatment effects of topical 5-fluorouracil 0.5% with other agents: odds of complete clearance by patient assessment[2]

5-Fluorouracil 0.5% vs comparative agents (4 studies; N=169)	No. of studies	No. of participants treated by comparative agent in all studies of review	Odds ratio (95% CI)
5-Fluorouracil 5%	2	44	0.21 (0.03–1.5)
Ingenol mebutate	14	1,411	4.1 (1.3–17)
Methyl aminolevulinate photodynamic therapy	7	557	4.2 (1.3–16)
Cryotherapy	2	174	5.3 (1.4–24)
3% Diclofenac in 2.5% hyaluronic acid	5	299	16 (4.4–63)

photodynamic therapy was more effective than cryotherapy (RR 1.3; 95% CI, 1.1–1.6). Comparisons among these studies were limited by varied length of follow-up and no standard methodology for measurement of treatment efficacy.[1]

A 2013 follow-up meta-analysis of 36 RCTs (N=6,473) from the prior Cochrane systematic review evaluated the relative efficacies of 8 treatments for actinic keratosis based on complete clearance according to patients.[2] Overall, 5-fluorouracil 5.0% was superior to all interventions except 5-fluorouracil 0.5% (see **TABLE 2**). The studies had a high risk of bias due to lack of randomization and allocation concealment details and selective reporting bias.

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What is the best treatment for adult somatization disorder?

EVIDENCE-BASED ANSWER

Psychological therapies, cognitive behavioral therapy (CBT), and enhanced care by the primary care physician (PCP) all have small positive effects in adults with somatization disorder (SOR: **B**, systematic review of low-quality RCTs). Yet, when compared with enhanced care, psychological therapies generally were not more effective. SSRIs/SNRIs and St. John's wort have moderate positive effects in reducing the severity of physical symptoms (SOR: **B**, systematic review of low-quality RCTs).

A 2014 Cochrane review of 21 RCTs (N=2,658 adults) evaluated nonpharmacological interventions for somatoform disorders and medically unexplained

physical symptoms in adults.[1] All studies evaluated the effectiveness of psychological therapy. Three separate analyses were described in this review: (1) psychological therapy versus usual care (not defined); (2) psychological therapy versus enhanced care, defined as care provided by the PCP that included patient education or structured counseling moments with the goal of providing the patient with tools for self-management; and (3) CBT versus behavioral therapy. Fourteen studies (n=1,440) evaluated forms of CBT; the remainder evaluated behavior therapies. The duration of interventions and specific techniques varied widely among studies. Only 1 study (n=173) compared CBT with behavior therapies.

For all studies comparing some form of psychological therapy with usual care, psychological therapy resulted in less severe somatic symptoms at the end of treatment, as measured by various self-reporting instruments (10 studies, n=1,081; standardized mean difference [SMD] –0.34; 95% CI, –0.53 to –0.16). This effect was small to moderate and the quality of evidence was considered low due to study heterogeneity. Subgroup analysis comparing CBT with usual care yielded similar results (6 studies, n=593; SMD –0.37; 95% CI, –0.69 to –0.05). The authors stated only CBT had been studied well enough for conclusions to be made of its efficacy. However, when compared with enhanced care, CBT was not more effective in terms of reducing somatic symptoms (3 studies, n=307; SMD –0.34; 95% CI, –0.71 to 0.03). Limitations of this review include small effect sizes, study heterogeneity, and inherent bias toward a favorable outcome as all participants in these studies were willing to receive psychological treatment.[1]

A separate 2014 Cochrane review examined pharmacological interventions for somatoform disorders in adults (26 RCTs, N=2,159).[2] Studies were rated as low quality secondary to concerns of bias and small sample sizes. SMDs were reported secondary to various somatization rating scales used in the different studies.

SSRIs and SNRIs (various medications and doses) compared with placebo were moderately effective for treating physical symptoms, anxiety, and depression in somatization disorders (3 studies, n=243; SMD –0.91; 95% CI, –1.36 to –0.46). SSRIs/SNRIs were no more effective than tricyclic antidepressants (TCAs) (3 studies, n=177; SMD –0.16; 95% CI, –0.55 to 0.23). TCAs were no more effective than placebo (2 studies, n=239; SMD –0.13; 95% CI, –0.39–0.13). Compared with placebo, St. John's wort was effective in reducing symptom severity (2 studies, n=322; SMD –0.74; 95% CI, –0.97 to –0.51).[2]

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Which treatment is best for hepatic encephalopathy due to end-stage liver disease?

EVIDENCE-BASED ANSWER

Rifaximin is as effective as other antibiotics or oral disaccharides for improving hepatic encephalopathy with a better safety profile (SOR: **A**, meta-analysis of RCTs). Combination therapy of rifaximin and lactulose is more effective for reversal of hepatic encephalopathy with less mortality than lactulose alone (SOR: **B**, RCT). Prophylactic use of rifaximin plus lactulose reduces hospitalizations for hepatic encephalopathy more than lactulose alone (SOR: **B**, RCT).

A 2012 meta-analysis of RCTs (12 trials, N=565; age >18 years) examined the efficacy of rifaximin 1,100 to 1,200 mg daily compared with oral disaccharides (lactulose or lactitol) or other antibiotics (neomycin and paromomycin) for treating reversible hepatic encephalopthy.[1] Rifaximin was compared with lactulose 45 to 120 mL/d, lactitol 60 g/d, neomycin 3,000 to 4,500 mg/d, or paromomycin 1,500 mg/d.

Primary outcomes were safety and effectiveness of rifaximin as measured by clinical improvement or resolution of encephalopathy using the Conn's score (or West Haven criteria) (see **TABLE**). Clinical improvement or resolution was defined as grade 0 or clinical improvement considered significant by primary investigators.[1]

Rifaximin, for clinical improvement or resolution of hepatic encephalopathy, was equivalent to monotherapy

TABLE

Conn's score (West Haven criteria) for hepatic encephalopathy[1]

Grade 0	No personality or behavioral abnormality
Grade 1	Trivial lack of awareness; euphoria or anxiety; shortened attention span; or impairment of ability to add or subtract
Grade 2	Lethargy; disorientation with respect to time; obvious personality change; or inappropriate behavior
Grade 3	Somnolence or semi-stupor; responsiveness to stimuli; confusion; gross disorientation; or bizarre behavior
Grade 4	Coma

with pooled data from disaccharides or other oral antibiotics (12 studies, n=477; odds ratio [OR] 1.96; 95% CI, 0.94–4.1) with fewer adverse events (9 studies, n=1,968; OR 0.27; 95% CI, 0.12–0.59). Adverse events analyzed were severe diarrhea beyond that expected of disaccharide use, abdominal pain, and the combination of nausea, anorexia, and weight loss. Combined analysis of all adverse events was used. Pooled data from 7 studies indicated no difference between rifaximin and nonabsorbable disaccharides (n=349 in resolution or clinical improvement of encephalopathy; OR 1.9; 95% CI, 0.79–4.7); data pooled from the 5 studies using rifaximin versus neomycin or paromomycin (n=128) also showed similar effectiveness (resolution or clinical improvement of encephalopathy) (OR 2.8; 95% CI, 0.35–22). Patients receiving rifaximin compared with all other treatments were less likely to experience diarrhea (OR 0.20; 95% CI, 0.04–0.92), but rates of abdominal pain, nausea, anorexia, and weight loss were similar.[1]

A 2013 prospective, double-blind RCT compared rifaximin (400 mg orally TID) plus lactulose (30–60 mL orally TID titrated to 2–3 stools per day) with lactulose plus placebo in 120 patients 18 to 80 years old with cirrhosis and overt hepatic encephalopathy as measured by West Haven criteria.[2] The primary outcome was reversal of encephalopathy using West Haven criteria (grade 0). Secondary endpoints included mortality within the first 10 days of hospitalization and length of hospital stay.

Combination therapy increased reversal of encephalopathy (76% vs 51%; *P*<.004) and shortened hospital stays (5.8 vs 8.2 days; *P*=.001). Combination therapy decreased mortality (24% vs 49%; *P*<.005) particularly due to sepsis (7 vs 17 patients; *P*=.01), with no difference in gastrointestinal bleeds or hepatorenal syndrome. Adverse events noted were diarrhea requiring lactulose adjustment and abdominal pain with rates similar in both groups.[2]

A 2010 randomized, double-blind placebo-controlled trial evaluated rifaximin (550 mg orally BID) or placebo for 6 months in 299 patients (age range 46–66 years) with chronic liver disease in remission from recurrent hepatic encephalopathy.[3] More than 90% of patients received concomitant lactulose therapy (mean dose 30 g/d). The primary endpoint was the first recurrence of encephalopathy, and the secondary endpoint was hospitalization for encephalopathy.

The rifaximin group reduced risk of breakthrough encephalopathy by 58% compared with the placebo group (hazard ratio [HR] 0.42; 95% CI, 0.28–0.64). Patients receiving rifaximin had fewer hospitalizations (14% vs 23%; HR 0.50; 95% CI, 0.29–0.80). Adverse events were similar in both groups.[3]

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How accurate are physical examination findings for diagnosing disc herniation?

EVIDENCE-BASED ANSWER

In patients with back pain and sciatica, the straight leg test has the best sensitivity (92%) for diagnosing disk herniation but has a specificity of only 28%. Specificities for other tests are better, with many at least 90%. The femoral nerve stretch test has the best specificity at 99%, but its sensitivity is only 17% (SOR: **A**, meta-analysis of cohort studies and single cohort study using CT and surgery as the gold standards for diagnosis).

A 2010 Cochrane review of 16 cohort studies (median 126 patients, range 71–2,504 patients) and 3 case control studies (range 38–100 cases) reported the sensitivity and specificity of physical findings for diagnosing disc herniation in patients complaining of low back pain and leg pain (sciatica).[1] Straight leg raise (SLR), crossed SLR, tendon reflexes, signs of weakness, muscle wasting, and sensory deficits were assessed using diagnostic imaging (CT or MRI) and intraoperative findings of disc herniation as the gold standard.

Of the physical examination assessments, SLR (passive elevation of leg on the symptomatic side with the patient in the supine position) was the most commonly assessed (15 trials; 7,233 patients) and showed the highest sensitivity of 92% (95% CI, 0.87–0.95), but poor specificity of 28% (95% CI, 0.18–0.40) as compared with surgical findings in a population with a more than 75% prevalence of lumbar disc herniation (see **TABLE 1**). In contrast, crossed SLR, (passive elevation of leg on asymptomatic side with patient in supine position) showed a low sensitivity of 28% (95% CI, 0.22–0.35), but a high specificity of 90% (95% CI, 0.85–0.94) in the same high prevalence setting. Other physical examination findings including scoliosis, muscle wasting, muscle weakness, impaired reflexes, and sensory deficits were less commonly assessed and had lower sensitivity and better specificity (see

TABLE 1

Sensitivity and specificity of physical examination findings in diagnosis of lumbar disc herniation[1]

Physical examination finding	Reference standard	No. of trials (patients)	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive likelihood ratio	Negative likelihood ratio
SLR	Surgical	9 (6,561)	0.92 (0.87–0.95)	0.28 (0.18–0.40)	1.28	0.29
Crossed SLR	Surgical	5 (2,950)	0.28 (0.22–0.35)	0.90 (0.85–0.94)	2.80	0.80
Paresis	MRI	1 (338)	0.27 (0.20–0.37)	0.93 (0.88–0.97)	3.86	0.78
Impaired Achilles reflex	MRI	1 (338)	0.15 (0.09–0.21)	0.93 (0.88–0.97)	2.14	0.91
Impaired Achilles reflex	Surgical	6 (4,177)	0.46 (0.29–0.62)	0.70 (0.50–0.89)	1.53	0.77
Forward flexion	Surgical	2 (104)	0.88 (0.85–0.90)	0.23 (0.16–0.29)	1.14	0.52
Extension test	CT or MRI	2 (183)	0.52 (0.13–0.90)	0.56 (0.17–0.94)	1.18	0.86

SLR=straight leg raise; ipsilateral pain with passive elevation of leg in supine position.
Crossed SLR=radicular pain with passive elevation of contralateral leg.
Paresis=weakness of ankle dorsiflexion (L4 radiculopathy) or extension of great toe (L5 radiculopathy).
Forward flexion=bending forward while standing.
Extension test=reproduction of usual pain with extension (while standing or lying prone).

TABLE 2

Sensitivity and specificity of physical examination findings compared with MRI/CT results in diagnosis of lumbar disc herniation[2]

Physical examination finding	Nerve root	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio	Negative likelihood ratio
Femoral nerve stretch test	L5	0.17 (0.07–0.33)	0.99 (0.94–1.00)	17.0	0.84
Sensory loss L4	L5	0.20 (0.10–0.37)	0.91 (0.83–0.95)	2.22	0.88
Hip flexion weakness	L5	0.23 (0.12–0.41)	0.93 (0.86–0.97)	3.29	0.83
Hip extension weakness	S1	0.18 (0.08–0.37)	0.90 (0.82–0.94)	1.80	0.91
Hip abduction weakness	L5	0.07 (0.02–0.21)	0.92 (0.84–0.96)	0.88	1.01
Hip abduction weakness	S1	0.04 (0.01–0.18)	0.91 (0.83–0.95)	0.44	1.05

TABLE 1). These results may not generalize to primary care settings given that most of the studies were performed in secondary care centers.[1]

A 2013 multicenter diagnostic cohort study evaluated the accuracy of physical examination findings for diagnosing disc herniation in 116 patients with unilateral lumbar radiculopathy of more than 12 weeks and 1 or more positive index tests.[2] MRI (94%) or CT (6%) were used as the gold standards, and index testing included SLR, femoral nerve stretch test, and muscle weakness. Patients had a mean age of 42 years and 59% were men; the mean duration of symptoms was 42 weeks.

Despite an overall prevalence of lumbar disc herniation of 78% (52% with nerve compression, 26% without), there was poor sensitivity and limited specificity of the physical examination findings (see **TABLE 2**).[2]

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

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Is behavioral activation an effective treatment for depression?

EVIDENCE-BASED ANSWER

Behavioral activation is moderately better than no treatment or usual care and at least as effective as antidepressant medication and cognitive behavioral therapy (CBT) for the treatment of depression (SOR: **B**, meta-analysis of low-quality heterogeneous RCTs and single RCT).

A 2014 meta-analysis assessed 26 RCTs (N=1,188) comparing behavioral activation with antidepressant medications, and with 3 types of control groups: (1) waitlist controls, (2) "usual care" for depression ranging from self-help to professional counseling, and (3) psychological "placebo" interventions including supportive counseling and some cognitive therapies.[1] Primary outcomes were self-rated and/or clinician-rated symptom levels pre- and posttreatment with follow-up ranging from postintervention to 49 weeks. Twenty-five studies compared behavioral activation with control groups across 31 comparisons and 1,088 participants in adult populations including general public, university students, older adults, and women with postpartum depression.

Behavioral activation moderately improved depression symptoms postintervention (standardized mean difference [SMD] –0.74; 95% CI, –0.91 to –0.56; number needed to treat [NNT]=3). Moderate between-study heterogeneity of treatment effects was found. Follow-up results between 6 to 9 months still showed behavioral activation somewhat superior to controls (SMD –0.35; 95% CI, –0.59 to –0.11; NNT=6).[1]

Four studies compared behavioral activation with antidepressant medication (n=283) in similar adult populations. Two studies used SSRIs and 2 studies used tricyclic antidepressants, with no apparent relationship between medication type and effect size. Postintervention, behavioral activation showed small but significant superiority to medication (SMD –0.42; 95% CI –0.83 to –0.00; NNT=5). When the 2 low-quality studies using tricyclics were excluded, this difference disappeared (SMD –0.38; 95% CI, –1.2 to 0.47). No long-term follow-up was measured, doses were not listed, and postintervention follow-up protocols were not detailed. Overall, many of the studies were small and of poor quality; only 7 studies reported 3 or more of 5 commonly accepted standards for RCTs.[1]

A 2013 systematic review evaluated studies comparing behavioral therapies with other psychological therapies for acute depression.[2] A single RCT (not included in the above meta-analysis) was identified as assessing efficacy specifically for behavioral activation. This trial evaluated behavioral activation against CBT and cognitive therapy (N=149) in a community sample of adult outpatients diagnosed with depression. Outcomes were measured through self-rated depression symptom levels (using the Beck Depression Inventory or the Hamilton Depression Rating Scale) pre- and posttreatment, with follow-up at 6, 12, 18, and 24 weeks. Acceptability was assessed by looking at participant attrition.

Results showed no significant differences between groups in efficacy or acceptability at any of the follow-up intervals.[2]

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Does intra-articular steroid injection in combination with physical therapy improve outcomes for patients with adhesive capsulitis?

EVIDENCE-BASED ANSWER

Patients with adhesive capsulitis (frozen shoulder) treated with steroid injection plus physical therapy showed significant improvement in active range of motion at 6 weeks compared with patients given steroid injection alone, but the combination provided no long-term improvement. Physical therapy plus steroid injection compared with placebo significantly improved function, active range of motion, and pain at 6 weeks, but only active range of motion continued to be improved at 3 to 6 months. In patients with physical therapy plus steroid injection versus physical therapy plus placebo, function and pain were significantly improved at 6 weeks, and only pain was significantly improved at 3 to 6 months (SOR: **A**, systematic review of RCTs).

A 2014 Cochrane review of 32 RCTs (N=1,836, aged ≥16) evaluating patients with adhesive capsulitis of any duration reviewed the effectiveness of physical therapy with and without intra-articular steroid injections.[1] Adhesive capsulitis was diagnosed by the clinicians. Patients with a history of trauma, osteoarthritis, rheumatoid arthritis, and myofascial neck or shoulder pain were excluded. Physical therapy included manual therapy, mobilization, exercise, therapeutic ultrasound, and laser therapy. Average treatment of physical therapy was 4 weeks. Outcomes measured were improvement of overall pain, function, quality of life, and range of motion.

At 6 weeks, physical therapy plus steroid injection showed a significant improvement in active range of motion compared with steroid injection alone, but no difference in function, pain, or quality of life (see **TABLE**). No difference was noted in any reported outcome at 3 to 6 months. When comparing physical therapy plus steroid injection with placebo injection alone, significant improvement was noted in function, active range of motion, and pain at 6 weeks. However, only active range of motion continued to be significantly improved at 3 to 6 months. A limitation to this

TABLE

Effect of adhesive capsulitis treatments of physical therapy and intra-articular glucocorticoid injection vs controls or placebo on function, quality of life, range of motion, and pain at 6 weeks and 3 to 6 months

Intervention	Outcome	Data source	Duration (weeks)	MD (95% CI)	SMD (95% CI)
PT + steroid vs steroid[1]	Function	2 RCTs, n=78	6		–0.35 (–0.80 to 0.10)
		1 RCT, n=74	26		–0.10 (–0.56 to 0.36)
	Quality of life, 36 item (total score not reported)	1 RCT, n=44	6	2.0 (–3.3 to 7.3)	
			26	–1.3 (–6.6 to 4.0)	
	Active ROM[a] (degrees)	1 RCT, n=44	6	32 (5.3–58)	
			26	21 (–5.2 to 47)	
	Overall pain	2 RCTs, n=78	6		–0.32 (–0.77 to 0.13)
		2 RCTs, n=74	26		–0.05 (–0.51 to 0.40)
PT + steroid vs placebo[1]	Function	1 RCT, n=78	6		–0.99 (–1.5 to –0.51)
		1 RCT, n=73	26		–0.36 (–0.83 to 0.11)
	Quality of life, 36 item (total score not reported)	1 RCT, n=44	6	3.9 (–1.4 to 9.2)	
			26	2.0 (–3.3 to 7.3)	
	Active ROM (degrees)	1 RCT, n=44	6	59 (33–85)	
			26	48 (29–67)	
	Overall pain	1 RCT, n=78	6		–0.78 (–1.5 to –0.04)
		1 RCT, n=73	26		–0.18 (–1.1 to 0.68)
PT + steroid vs PT + placebo[2]	Shoulder disability questionnaire (0 to 100 mm VAS)	1 RCT, n=80	6	–4.3 (–7.8 to –0.84)	
			26	–2.0 (–6.0 to 2.0)	
	Shoulder pain and disability index (0 to 50 points)	1 RCT, n=93	6	–24 (–38 to –10)	
			26	–9.4 (–23 to 4.6)	
	Overall pain	2 RCTs, n=84	6		–0.86 (–1.3 to –0.47)
		3 RCTs, n=128	12		–0.57 (–0.94 to –0.20)

[a]Active ROM=sum of amplitudes of movement in flexion, abduction, and external rotation in degrees.
MD=mean difference; PT=physical therapy including manual therapy and home exercises; ROM=range of motion in degrees of flexion, abduction, and external rotation; SMD=standard mean difference; VAS=visual analog scale.

study included heterogeneity of reporting and improvement outcomes, and variation of steroid and insertion site for injection.[1]

A 2012 systematic review of 32 studies (N not reported) consisting of RCTs and case studies of adults with adhesive capsulitis with a mean duration of 13 to 21 weeks evaluated combinations of physiotherapy, steroid injection, and/or placebo.[2] Adhesive capsulitis was diagnosed based on clinical signs and symptoms (range of motion and pain), lab tests, and radiography. Patients' mean ages were 54 to 57 years, and 42% to 63% of study patients were women.

Physical therapy included exercise, mobilization, and stretching. Patients without physical therapy received passive treatments including laser therapy, TENS, ultrasound, heat, or ice. Steroid injections were either 20 mg triamcinolone hexacetonide or 40 mg methylprednisolone acetate. Function and disability was measured with the Shoulder Pain and Disability Index (SPADI) and the Shoulder Disability Questionnaire (SDQ). Pain assessment was measured with a 0–100 mm visual analog scale (VAS), Likert scale, and SPADI-5 item pain subscale. Three RCTs with 128 patients compared physical therapy plus steroid injection to physical therapy plus placebo.[2]

Function and pain significantly improved in the physical therapy plus steroid injection group at 6 weeks, while pain significantly improved at 3 to 6 months, but not function

(see **TABLE**). This study was limited by a small number of patients, use of different reporting scales and time frames, and heterogeneity of studies.[2]

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Does early detection of renovascular hypertension improve outcomes?

EVIDENCE-BASED ANSWER

Probably not. Finding atherosclerotic renal artery stenosis (ARAS) and treating with revascularization has shown no clinically significant improvement in rates of myocardial infarction (MI), renal function, congestive heart failure (CHF), or stroke compared with medical treatment of renovascular hypertension (SOR: **A**, meta-analysis of RCTs). Recommendations to revascularize asymptomatic ARAS are controversial, calling into question the need for early detection (SOR: **C**, expert opinion).

A meta-analysis of 7 RCTs (N=2,139) compared medical therapy versus revascularization in patients with ARAS for complications such as worsening renal failure, nonfatal MI, systolic blood pressure change, CHF, stroke, and death.[1] Only 2 trials reported the degree of ARAS (50% and 60%). Medical therapy consisted of antihypertensive medication (eg, beta-blockers, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, or angiotensin II receptor blockers), statins, antiplatelet agents, and lifestyle modification including smoking cessation. Patients who underwent revascularization had either angioplasty or stenting and also received optimal medical treatment. Patients were followed for 1 to 43 months.

Slightly fewer antihypertensive medications were needed in the patients undergoing revascularization than among patients receiving medical therapy only (5 trials, n=2,035; mean difference [MD] –0.18; 95% CI, –0.27 to –0.09). No difference was noted between revascularization plus medical therapy versus medical therapy alone, for the following outcome measures: nonfatal MI (6 trials, n=2,109; odds ratio [OR] 0.99; 95% CI, 0.69–1.4), renal function changes (7 trials, n=2,139; OR 0.92; 95% CI, 0.74–1.1), mortality (4 trials, n= 1,929; OR 0.91; 95% CI, 0.72–1.1), CHF hospitalizations (3 trials, n=1,877; OR 1.2; 95% CI, 0.84–1.6), or stroke (4 trials, n=1,929; OR 1.1; 95% CI, 0.72–1.7).[1]

The 2005 American College of Cardiology and American Heart Association evidence-based guideline on management of patients with peripheral artery disease recommended diagnostic studies in patients with early- or severe-onset hypertension (level of evidence [LOE] B, "single randomized trial or nonrandomized studies") or hypertension that is suddenly worse, treatment resistant, or malignant (LOE C, "consensus opinion of experts, case studies, or standard-of-care").[2] The guideline also recommended diagnostic studies in patients with azotemia after taking ACE inhibitors or angiotensin receptor blockers, unexplained atrophic kidney, or sudden unexplained pulmonary edema (LOE B).

The guideline's recommendation to screen for ARAS was based on a presumption that revascularization would improve blood pressure control, preserve renal function, and prevent cardiovascular complications. However, for asymptomatic patients, the guideline stated, "Recommendations regarding the role of percutaneous revascularization of asymptomatic renal disease are made largely on the basis of expert opinion and are not based on evidence that treatment of asymptomatic RAS improves any renal or systemic outcome, including renal preservation, blood pressure, or cardiovascular morbidity or mortality. Therefore, these recommendations are still considered controversial and must be individualized for the patient by each treating physician."[2]

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Do anabolic steroids help improve recovery from hip fractures in the elderly?

EVIDENCE-BASED ANSWER

The anabolic steroid, nandrolone, alone or in combination with a protein supplement, improves speed of gait and quality of life and preserves lean body mass. However, nandrolone has no effect on pain, independence in activities of daily living (ADLs), or the combined outcome of mortality and need for higher level of care on discharge (SOR: **B**, small RCTs).

An RCT of 63 women (mean age 81 years) living independently after hip fracture examined the effect of anabolic steroids on function and pain.[1] Patients were randomized to intramuscular (IM) nandrolone decanoate (25 mg every 3 weeks) for 1 year with vitamin D3 (0.25 mcg daily) and calcium (500 mg daily) or to control (calcium 500 mg daily). The speed of gait was evaluated in a corridor 30 meters long; pain was assessed by a 1 to 10 visual analog scale (VAS).

Compared with the control group, the anabolic steroid group had an increased mean gait speed (30 seconds per 30 m vs 46 seconds per 30 m, respectively; *P*=.009), but had no significant change in mean pain score (6.5 vs 5.0; *P*=.80).[1]

An RCT of 60 women with a femoral neck fractures examined the effect of protein-rich liquid supplementation, alone or in combination with anabolic steroids, on body composition and function over 6 months.[2] The women were all older than 70 years with femoral neck fractures treated with internal fixation. They received a protein-rich supplement alone, the supplement with nandrolone decanoate 25 mg IM every third week, or standard treatment (control). All patients also received vitamin D (400 IU) and calcium (1,000 mg) per day. Outcomes assessed were body composition, ADLs, and health-related quality of life at 6 months. ADLs were measured by the Katz index of independence in 6 ADLs (score of 6=patient independent; 0=patient very dependent). Quality of life was measured using Euro Quality of Life scale (EuroQol), which assesses activities, pain, mood, mobility, and self-care.

At 6 months, the protein plus anabolic steroid group had an increase in lean body mass of 0.27 kg compared with decreases of 1.3 kg in the protein-supplement-alone group and 1.2 kg in the control group (*P*<.05 for comparison of steroid vs other groups). At 6 months, more patients in the protein plus steroid and the protein-supplement-alone groups were independent in ADLs (Katz index score of 5–6) than in the control group (*P*<.005 and .05, respectively, exact numerical results not reported). Anabolic steroid use (vs control) was associated with an increased odds ratio (OR) for any improvement in EuroQoL at 6 months (OR 17; 95% CI, 1.1–256), an effect not seen with protein supplementation alone.[2]

An RCT of 29 elderly women (mean age 82 years) with hip fractures examined the effect of weekly injections of nandrolone 2 mg/kg given for 4 weeks or placebo on the combined outcome of need for a higher level of care at discharge and mortality.[3] No significant difference was noted between groups in the numbers discharged to a higher level of care or mortality (risk ratio 0.75; 95% CI, 0.42–1.3). No power calculation was performed so the sample size may have been too small to detect a difference.

The quality of the evidence from all 3 studies was low due to poor randomization and lack of allocation concealment and unclear blinding.

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What are the benefits and harms of testosterone replacement therapy (TRT) in men with low testosterone?

EVIDENCE-BASED ANSWER

In men with low testosterone and type 2 diabetes mellitus (DM2) or metabolic syndrome, TRT improves glycemic control, triglyceride levels, and body composition (SOR: **C**, meta-analysis of disease-oriented outcomes from RCTs). In men with low testosterone and frailty or low mobility, TRT does not result in clinically relevant improvements in muscle strength, body composition, or quality of life (SOR: **B**, 2 RCTs, 1 stopped early due to an increase in adverse cardiovascular events in TRT users). TRT is associated with an increased risk of death, myocardial infarction (MI) or stroke after adjustment for baseline comorbidities (SOR: **B**, one retrospective cohort).

A 2013 systematic review and meta-analysis of 9 RCTs (N=627) studied the effects of TRT on men with late-onset hypogonadism (LOH) and metabolic syndrome or DM2.[1] LOH is most commonly defined as a syndrome of total testosterone level of less than 11 nmol/L plus erectile dysfunction, decrease in morning erections, and decrease in sexual thoughts; however, the RCTs used total testosterone cutoff levels ranging from 8 to 15 nmol/L. One of the RCTs used a free testosterone level of less than 225 pmol/L as the cutoff. TRT was dosed orally in 4 trials, via transdermal gel in 3 trials, and via intramuscular injection in 2 trials. For men with metabolic syndrome, multiple metabolic measurement were followed for a mean of 57 weeks (range 30–104 weeks). Men with DM2 were followed for a mean of 28 weeks (range 12–52 weeks).

In the men with metabolic syndrome, TRT reduced fasting plasma glucose (FPG), triglyceride levels, and waist circumference (see **TABLE 1**). In the men with DM2, TRT reduced FPG, HbA1C, and triglyceride levels (see **TABLE 2**). No adverse effects of TRT were reported.[1]

A 2010 RCT of elderly men (N=274) with LOH investigated the effects of TRT on physical frailty.[2] All patients were older than 65 years (mean age 73 years), and were diagnosed with LOH using a total testosterone level of less than 12 nmol/L or free testosterone level of less than 250 nmol/L. They exhibited at least 1 symptom of frailty defined as unintentional weight loss, self-reported exhaustion, low physical activity, slow walk time, or low handgrip strength. Patients applied 50 mg testosterone gel or matching placebo once a day for 6 months. After 10 days and again after 3 months of treatment testosterone levels were measured and the dose was adjusted to 25 or 75 mg as needed to target serum levels of 18 to 30 nmol/L. Muscle strength, body composition, overall physical functioning, and quality of life were measured at baseline and again after using TRT for 6 months. Because abnormal glucose metabolism was not an inclusion criterion, this RCT was excluded from the 2013 meta-analysis.

TRT increased isometric knee extension peak torque compared with placebo (mean difference [MD] 8.6 newton-meters; 95% CI, 1.3–16); however, all other measures of muscle strength and physical function were unchanged. TRT increased lean body mass (MD 1.1 kg; 95% CI, 0.6–1.5) and decreased fat mass (MD –0.6 kg; 95% CI, –1.1 to –0.1). The Aging Males Symptoms scale (range 17–85) showed minor improvement on the somatic subscale (MD –1.2; 95% CI, –2.4 to –0.04) and the sexual subscale (MD –1.3; 95% CI, –2.5 to –0.2).[2]

A 2010 RCT (N=209) investigated the rate of adverse events in men with limited mobility and low testosterone.[3] Men (mean age 74 years) with LOH (total testosterone level 3.5–12 nmol/L or free testosterone <173 nmol/L) received TRT or placebo for 6 months. No significant differences were noted at baseline in age, BMI, race, total testosterone level, or strength testing. The investigators noted a higher incidence of hyperlipidemia (63% vs 50%; *P*=.05) and statin therapy (62% vs 47%; *P*=.03) in the TRT group at baseline. Patients applied 100 mg testosterone gel or matching placebo once a day for 6 months. After 2 weeks of treatment, testosterone levels were measured and the dose was adjusted to 50 or 150 mg to target serum levels of 17 to 35 nmol/L. This RCT was also excluded from the 2013 meta-analysis.

TRT increased leg-press force (129 newtons; 95% CI, 44–215) and chest-press force (35 newtons; 95% CI, 13–56) compared with placebo. No improvement occurred in grip strength, 50-meter walking speed, stair-climbing power, or repeated lifting and lowering. The trial was stopped before completing enrollment (N=252) when a safety analysis found significantly higher rates of cardiovascular adverse

TABLE 1

Effects of TRT in men with LOH and metabolic syndrome[1]

Measurement	No. of trials	N	Mean difference	95% CI
Fasting plasma glucose (mg/dL)	5	471	–8.6	–14 to –3.4
Triglyceride (mg/dL)	6	483	–7.2	–12 to –2.5
Waist circumference (cm)	6	483	–4.1	–7.8 to –0.30

LOH=late-onset hypogonadism; TRT=testosterone replacement therapy.

TABLE 2

Effects of TRT in men with LOH and type 2 diabetes mellitus[1]

Measurement	No. of trials	N	Mean difference	95% CI
Fasting plasma glucose (mg/dL)	5	263	–20	–32 to –6.3
HbA1C (%)	5	263	–0.62	–1.0 to –0.24
Triglyceride (mg/dL)	5	263	–11	–15 to –6.7

HbA1C=glycosylated hemoglobin; LOH=late-onset hypogonadism; TRT=testosterone replacement therapy.

TABLE 3

Risk of death, MI, or stroke in veterans treated with TRT[4]

	Cumulative rate of adverse events (%)			
Years of follow-up	TRT nonusers	TRT users	Risk difference (%)	95% CI
1	10	11	1.3	–7.1 to 9.7
2	15	19	3.1	–4.9 to 11
3	20	26	5.8	–1.4 to 13

MI=myocardial infarction; TRT=testosterone replacement therapy.

events including chest pain, MI (1 fatal), atrial fibrillation with rapid ventricular response, heart failure exacerbation, new-onset heart failure, hypertension, stroke, new ischemic ECG changes, and syncope in the TRT group (relative risk 5.4; 95% CI, 2.0–15).[3]

A 2013 retrospective cohort study of Veterans Administration patients evaluated adverse outcomes associated with TRT.[4] All men had an initial total testosterone level of less than 300 ng/mL and underwent coronary angiography between 2005 and 2011. TRT users who filled a prescription for gel, patch, or injection (n=1,233; mean age 61 years) were compared with TRT nonusers (n=7,486; mean age 64 years).

TRT users were more likely to be obese, but had significantly lower rates of obstructive coronary artery disease, hypertension, hyperlipidemia, heart failure, prior MI, COPD, peripheral vascular disease, and cerebrovascular disease. Compliance with TRT and dose-response were not evaluated. Patients were followed for an average of 28 months. Although adverse outcomes (death, MI, or stroke) were more common in TRT users, the differences did not reach statistical significance (see **TABLE 3**). After adjusting

for the differences in baseline comorbidities, TRT use was associated with an increased risk of adverse outcomes compared with nonuse (hazard ratio 1.3; 95% CI, 1.1–1.6).[4]

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What is the role of helminth therapy for inflammatory bowel disease?

EVIDENCE-BASED ANSWER

Evidence is insufficient to recommend helminth therapy for inflammatory bowel disease (IBD) (SOR: **B**, systematic review of 2 small RCTs and a single RCT).

Helminth therapy—administering the ova of parasites to stimulate an immune reaction—is an increasingly studied intervention for IBD.

A 2014 Cochrane review assessed studies comparing the helminth *Trichuris suis* ova (TSO, porcine whipworm, which is not considered a human pathogen) with placebo treatment in patients with IBD.[1] Studies commonly used as an outcome measure the Ulcerative Colitis Disease Activity Index (UCDAI, full range 0–12 points, in which a total score of 0–2 was remission; 3–6, mild disease; 7–10, moderate disease; and >10, severe disease).

One RCT in this review (n=54; age range 18–72 years) compared treatment with 2,500 TSO every 2 weeks for 12 weeks with a placebo in patients with ulcerative colitis and an UCDAI of at least 4. Although UCDAI symptom scores improved in the treatment group (mean difference [MD] –1.4; 95% CI, –1.8 to –1.1), clinical improvement and remission rates did not reach statistical significance (relative risk [RR] 2.6; 95% CI, 0.97–7.0 and RR 2.4; 95% CI, 0.27–22, respectively). The second RCT in the review (n=36; age range 18–55 years) compared the safety and tolerability of TSO at various single-dose regimens (500, 2,500, and 7,500 ova) with placebo in patients with symptoms of Crohn's disease of at least 3 months' duration. No significant differences were noted in adverse events between the groups (RR 0.83; 95% CI, 0.35–2.01).[1]

A study of TSO in Crohn's disease reported only in a 2013 press release (double-blinded RCT, N=250) compared the Crohn Disease Activity Index score (CDAI, a self-reported scale of 8 weighted factors, scored from 0 to 600) in patients with moderate-to-severe Crohn's disease who were treated with 7,500 TSO every 2 weeks for 12 weeks with the CDAI of similar patients given placebo.[2] The treatment group did not demonstrate a significant response (100-point decrease in CDAI) or evidence of remission (CDAI ≤150) compared with the placebo group. EBP

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

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