

EVIDENCE-BASED PRACTICE

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Pet squirrels

My father decided he wanted to raise a pair of chinchillas (*Chinchilla lanigera*)—those large, fluffy ground squirrels native to the Andes. Known for their high-quality pelts, they make extremely low-quality pets, as we found out. Our pair went berserk when anyone got near their cage—bouncing off the sides and top and gyrating around inside like 2 furious electrons. With patience, you could get one out and pet it, but you had to keep hold of its tail or it shot out of your hands. Of course, being rodents, they had babies. I have to say, baby chinchillas are cute—psychotic, but cute. I concluded that keeping exotic squirrels as pets was a bad idea.

That notion was reinforced when I read a case series of 3 men living in Germany who developed fatal encephalitis from an unknown pathogen.¹ These men knew each other and they all bred exotic rodents! Postmortem analysis showed that they carried a bornavirus present in variegated squirrels (*Sciurus variegatoides*), a rather pretty tree squirrel found in Central American forests. Circumstantial evidence suggested the squirrel bornavirus was the lethal pathogen. The researchers called the agent “variegated squirrel 1 bornavirus” (or VSBV-1). Fortunately for the rest of us, there was no evidence of person-to-person transmission.

I now have another reason not to get a squirrel, exotic or otherwise. Still, this case reminds me that people love owning exotic animals, despite the potential downsides. My father, for example, also tried to make house pets of 4 desert tortoises (*Gopherus agassizii*), 3 great horned owls (*Bubo virginianus*), 2 coyotes (*Canis latrans*), an epileptic skunk (*Mephitis mephitis*), and a ferocious badger (*Taxidea taxus*). Each one, for its own reasons, made a terrible pet, but that never dimmed my father’s interest in cozying up with something new and wild.

Be grateful, then, for the science of microbiology and Koch’s postulates. Since human beings seem determined to keep wacky pets, let’s gather all the evidence we can to mitigate any biological risks. After all, even “harmless” kittens carry *Bartonella henselae*.



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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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In patients with osteoporosis, should subclinical hyperthyroidism be treated?

EVIDENCE-BASED ANSWER

Subclinical hyperthyroidism with thyroid-secreting hormone (TSH) ≤ 0.45 mIU/L is associated with an increased fracture rate (SOR: **A**, meta-analysis of cohort studies), but treatment of subclinical hyperthyroidism when TSH is ≤ 0.2 mIU/L only slightly increases bone mineral density (BMD) (SOR: **C**, case-control study with disease-oriented outcomes). Current guidelines recommend clinicians “strongly consider” treatment of subclinical hyperthyroidism in patients with osteoporosis and TSH persistently < 0.1 mIU/L (SOR: **C**, expert opinion).

Evidence summary

A 2015 meta-analysis of 13 prospective published and unpublished cohort studies (N=70,298) assessed the association of subclinical hyperthyroidism with hip (primary outcome), nonspine, spine, or any fractures.¹ Cohort studies with baseline thyroid testing and subsequent fracture assessment were included. Studies with only overtly hyperthyroid patients or patients on thyroid-altering medication were excluded.

Median patient age was 64 years, 61% were women, and the median follow-up was 12.1 years. All fractures were confirmed by x-ray, whereas spine fractures also required clinical diagnosis. Overall, 3.2% of patients had subclinical hyperthyroidism (TSH < 0.45 mIU/L and normal thyroxine [T4]), with 2.4% with “low” TSH (0.10–0.44 mIU/L) and 0.8% with “suppressed” TSH (< 0.10 mIU/L).¹

Patients with subclinical hypothyroidism had an increased risk of hip fractures (12 studies, n=64,691; hazard ratio [HR] 1.4; 95% CI, 1.1–1.6) and any fractures (8 studies, n=28,516; HR 1.3; 95% CI, 1.1–1.5) compared with euthyroid patients, when adjusted for age and sex. No differences were noted in spine fractures. The quality of many of the studies was considered to be good (population based, risk factor controlled, formal fracture adjudication, blinded fracture assessment, excellent follow-up), with minimal heterogeneity.¹

A 2008 case-control study (21 cases and 36 controls) compared BMD between patients treated for subclinical hyperthyroidism (TSH < 0.2 mIU/L and normal T4) and matched controls.² Case and control patients were women matched for age by decade, with a mean age of 50 years. Cases were recruited from a tertiary care thyroid clinic; controls from the health system. Seventeen cases had been treated with radioiodine ablation and 3 with thyroidectomy (data on 1 patient not reported).

BMD increased by 1.5% in patients with subclinical hyperthyroidism who were treated, when measured 6 months or longer after thyroid function had normalized ($P < .05$). Change in BMD for controls was not statistically significant (numeric data not presented). This study was limited by lack of randomization, small sample size, and lack of fracture data.²

Recommendations from others

The 2011 American Thyroid Association and American Association of Clinical Endocrinologists evidence-based guidelines recommended clinicians “strongly consider” treatment of persistent subclinical hyperthyroidism (TSH < 0.1 mIU/L for 3–6 months) in individuals with osteoporosis (Grade 2/++: weak recommendation based on moderate quality evidence).³ For patients with persistent low normal TSH (0.1–0.44 mIU/L), clinicians should “consider” treatment of subclinical hyperthyroidism in patients with osteoporosis (Grade 2/+ : weak recommendation based on low-quality evidence). **EBP**

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Melatonin; it ain't just for sleep anymore

Gonçalves AL, Martini Ferreira A, Ribeiro RT, et al. Randomised clinical trial comparing melatonin 3 mg, amitriptyline 25 mg and placebo for migraine prevention. *J Neurol Neurosurg Psychiatry*. 2016; pii: jnnp-2016-313458.

An RCT compared the effectiveness of melatonin with amitriptyline and placebo for migraine prevention in 196 adult patients with chronic migraines. Patients had a history of at least 3 migraine attacks or 4 migraine headache days per month. Patients were randomized to either melatonin 3 mg, amitriptyline 25 mg, or matching placebo nightly.

In an intention-to-treat analysis, compared with placebo at 12 weeks, headache days per month were reduced in both the melatonin group (6.2 vs 4.6 days; mean difference [MD] -1.6; 95% CI, -2.4 to -0.9) and amitriptyline group (6.2 vs 5.0 days; MD -1.1; 95% CI, -1.5 to -0.7). Mean headache intensity (0–10 pain scale) was also lower at 12 weeks in the melatonin group (4.8 vs 3.6; MD -1.2; 95% CI, -1.6 to -0.8) and in the amitriptyline group (4.8 vs 3.5; MD -1.3; 95% CI, -1.7 to -0.9) compared with placebo. No difference was noted between the melatonin and amitriptyline groups for either outcome. The melatonin group had more patients with >50% improvement in headache frequency than the amitriptyline group (54% vs 39%; $P<.05$).

Adverse events were reported more often in the amitriptyline group than the melatonin group (46 vs 16 events; $P<.03$) with daytime sleepiness the most common complaint. No difference was noted for the number of adverse events with melatonin and placebo (16 vs 17; $P=NS$). Overall, 69% to 75% of patients in all groups completed all 3 months of the trial.

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

Bottom line: Melatonin is an option for migraine prophylaxis, as it appears as effective as amitriptyline for migraine prevention with fewer adverse effects.

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A shot in the arm for renal colic: diclofenac feels the best

Pathan SA, Mitra B, Straney LD, et al. Delivering safe and effective analgesia for management of renal colic in the emergency department: a double-blind, multigroup, randomised controlled trial. *Lancet*. 2016; 387(10032):1999–2007.

This double-blind 1:1:1 RCT (N=1,645) compared diclofenac 75 mg intramuscular (IM) versus morphine 0.1 mg/kg intravenous (IV) versus paracetamol 1 g IV in patients with suspected renal colic presenting to the emergency department of an academic tertiary care hospital in Qatar.

The primary outcome for this study was the proportion of patients achieving $\geq 50\%$ reduction in the initial pain score (0–10 scale) 30 min after medication administration. Secondary outcomes included mean pain score at 30 min, proportion with ≥ 3 -point drop in pain score, need for rescue analgesia, proportion with pain score >2 at 60 min, and adverse events.

The primary outcome was achieved in 68% in the diclofenac group, 66% in the paracetamol group, and 61% in the morphine arm ($P<.04$ for 3-way comparison). Rescue analgesia was required more with morphine than diclofenac (23% vs 12%; odds ratio (OR) 2.3; 95% CI, 1.7–3.2) or paracetamol (23% vs 20%; OR 1.9; 95% CI, 1.4–2.8). The proportion of patients with pain scores >2 at 60 min after rescue medication was significantly higher in the morphine group (38%) than the diclofenac (24%) and paracetamol groups (30%) ($P<.001$ for 3-way comparison).

Compared with morphine, there were fewer adverse events with diclofenac (3% vs 1%; OR 0.3; 95% CI, 0.1–0.8) and paracetamol (3% vs 1%; OR 0.4; 95% CI, 0.2–0.9).

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

Bottom line: IM diclofenac is more effective than IV morphine or IV paracetamol at providing short-term pain relief (50% reduction in pain within 30 minutes of administration) in patients with symptoms of renal colic. Both diclofenac and paracetamol are associated with fewer adverse events than morphine. However, IM diclofenac is not available in the United States and it is not known if other IM NSAIDs would have the same effect.

EBP

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In older adults with depression, is aerobic exercise safe and effective?

CASE

A 68-year-old woman is found to have a geriatric depression scale (GDS) score of 9 at her annual wellness visit. With obtaining more history, you diagnose moderate depression. She wants to know if exercise might help her depression.

Bottom line

In older adults with mild-to-moderate baseline depression and no contraindications, moderate-intensity aerobic exercise can be an effective treatment, leading to a clinically significant reduction in depression rating scale scores.

Evidence summary

A 2013 Cochrane review of 39 RCTs with 2,326 participants with depression compared exercise with control interventions or psychotherapy.¹ The 35 trials (1,356 participants) comparing exercise with no treatment or a control intervention showed an overall 38% improvement (standardized mean difference [SMD] -0.62 ; 95% CI, -0.81 to -0.42).

Including only the 6 trials (464 participants) with adequate blinding and intention-to-treat analysis, outcomes were not significantly different for exercise, psychotherapy, pharmacologic therapy, or placebo (SMD -0.18 ; 95% CI, -0.47 to 0.11). Exercise was moderately more effective than a control intervention for reducing symptoms of depression, but analysis of methodologically robust trials showed only a small effect in favor of exercise.¹

A 2012 meta-analysis designed to estimate the effect of exercise on depressive symptoms in older people identified 7 eligible RCTs (mean age >60 years, follow-up >3 months, and identification and rating of pretest depression severity) with 556 participants ≥ 60 years.² The 7 RCTs showed that moderately intense exercise consisting of three to five 30- to 45-min sessions per week for 3–4 months provided a small reduction in depressive symptoms based on validated rating scales (SMD 0.34 ; 95% CI, 0.17 – 0.52).

A large systematic review and meta-analysis including 90 RCTs with 10,534 sedentary patients with chronic illness found that exercise reduced depressive symptoms based on depression scales (heterogeneous mean effect size delta 0.30 ; 95% CI, 0.25 – 0.36 ; NNT=6).³ A greater effect was demonstrated for moderate or vigorous

activity alone (delta 0.46 vs 0.24 for controls; $P=.001$). These effects were greatest among patients with higher baseline depressive symptoms and more physical activity. The mean exercise training was 42 minutes, 3 times a week.

An RCT of 57 community-dwelling Taiwanese adults (mean age 77 years) with depressive symptoms and a GDS score of >5 (on a 0 to 15 scale, with higher numbers indicating more disease and scores >5 indicating depression) examined the effects of 12 weekly cognitive behavioral therapy group sessions 60–80 min long versus a 12-week aerobic exercise program consisting of 150 min per week or placebo.⁴ Participants were followed for 9 months.

The aerobic exercise group and therapy showed significant reduction of GDS ratings by 4.0 and 3.5 points, respectively, versus to 2.0 points in the control group ($P=.012$) immediately after the exercise intervention, which attenuated to 4.21 and 2.61 points versus 2.45 points ($P=.119$) at 3 months and 3.8 and 3.0 points versus 2.1 points ($P=.2$) at the 6-month follow-up. Compared with baseline, the exercise group showed statistically significant improvement in GDS scores at all 3 time points ($P=.03$, $P=.012$, and $P=.037$, respectively). The therapy group only showed improvement immediately after therapy of 3.5 GDS points ($P=.009$), and not at 3 or 6 months' follow-up ($P=.857$, and $P=.318$, respectively).⁴

CASE WRAP-UP

After careful discussion with your patient, you both agree that she will try a month of walking, 5 days per week for at least 30 minute a day. At 1 month, she returns to the clinic and her GDS score is now 3.

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What are the management recommendations for deer tick exposure?

EVIDENCE-BASED ANSWER

Single-dose doxycycline in a Lyme hyperendemic area decreases the incidence of erythema migrans in high-risk patients by 2.8% if given within 72 hours after an *Ixodes scapularis* tick bite (SOR: **B**, single RCT). Amoxicillin does not decrease the incidence of erythema migrans following an *I scapularis* tick bite (SOR: **B**, single RCT). Patients who develop possible symptoms of Lyme disease after tick removal should seek medical attention (SOR: **B**, evidence-based guideline).

An RCT (N=482), conducted between 1987 and 1996 in a Lyme disease hyperendemic area of New York, looked at the benefit of single-dose 200 mg doxycycline to prevent Lyme disease after a tick bite.¹ All patients had removed an attached *I scapularis* tick from their body within the prior 72 hours. Outcomes examined were the development of erythema migrans and serum antibody levels.

Patients receiving doxycycline compared with placebo had a decreased incidence of erythema migrans (0.4% vs 3.2%; $P=.04$; number needed to treat=36). All patients with erythema migrans had positive or equivocal serologies. No asymptomatic seroconversions occurred during this study. Doxycycline was associated with more frequent adverse effects, mostly gastrointestinal related (30% vs 11%; $P<.001$; number needed to harm=6) compared with placebo. Only 9 patients developed Lyme disease.¹

A double-blind RCT (N=387) from 1989 to 1991 in a Lyme-endemic region of Connecticut studied the effects of antibiotics for prophylaxis of Lyme disease after an *I scapularis* tick bite within the prior 72 hours.² Patients were randomly assigned to amoxicillin 250 mg 3 times a day or placebo for 10 days, and followed for 1 year. Outcomes assessed were for development of erythema migrans, as well as IgG and IgM antibody levels to *Borrelia burgdorferi* at baseline, 6 weeks, and 3 months.

Amoxicillin compared with placebo did not decrease the risk of erythema migrans (1.2% vs 0%; $P=.22$). No subjects had asymptomatic seroconversion and none developed late manifestations of Lyme disease.²

In their 2006 evidence-based guideline, the Infectious Diseases Society of America recommended 200 mg doxycycline for patients 8 years or older within 72 hours of tick removal if the following criteria are met: an adult or nymphal *I scapularis* tick has been attached for 36 or more hours, local tick infection rate with *B burgdorferi* is 20% or higher, and doxycycline is not contraindicated (B-I recommendation: moderately in favor, based on 1 or more RCTs).³ All patients with confirmed tick bites should seek medical attention if they develop erythema migrans or a viral illness within 30 days of a tick bite (A-II recommendation: strongly in favor, based on nonrandomized trials).

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What diagnostic testing, if any, is needed in pregnant women with asymptomatic elevated urobilinogen?

EVIDENCE-BASED ANSWER

Urine urobilinogen during pregnancy is not associated with hemolysis disorders (SOR: **C**, observational study). It has a low positive likelihood ratio for the detection of abnormal bilirubin and liver function tests (SOR: **C**, observational study extrapolated from nonpregnant patients).

A 1992 prospective observational study of hemolysis parameters for severe forms of hypertension during pregnancy at the University of Innsbruck, Austria, included 335 pregnant women in their second and third trimester (166 with a hypertensive disorder of pregnancy and 179 nonhypertensive controls).¹ The study used serial laboratory tests for urobilinogen, bilirubin, lactate dehydrogenase, fragmentocytosis, and decrease in hemoglobin >2 g/dL to identify hemolysis during pregnancy prior to

development of full clinical disease. Participants were divided into nonhypertensive; proteinuric; pregnancy-induced hypertension; mild preeclampsia; severe preeclampsia; and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome groups.

The median urobilinogen for all groups was 0 mg/dL, with ranges of 0–4 mg/dL in the nonhypertensive patients and HELLP patients; 0–1 mg/dL in the proteinuria and mild preeclampsia patients; and 0–8 mg/dL in the pregnancy-induced hypertension and severe preeclampsia groups (no *P* values given). The authors concluded that urobilinogen had poor sensitivity and specificity (no values given) as an early marker of hemolysis during pregnancy. Limitations of the study included that elevated urobilinogen (>4 mg/dL) was noted in patients with clinically severe hemolysis but also in urine contaminated with leukocytes, erythrocytes, or protein.¹

A 1987 prospective observational study enrolled 122 pediatric and adult emergency department patients (pregnancy status unknown) over a 5-month period in El Paso, Texas.² Eligible patients had symptoms warranting serum liver function tests (LFTs) and urinalysis performed during the same emergency department visit. The study investigated the correlation between urobilinogen and abnormal LFTs including aspartate aminotransferase, bilirubin, alkaline phosphatase, prothrombin time, or partial thromboplastin time.

Elevated urobilinogen >4 mg/dL showed a small increase in the likelihood of elevated serum bilirubin >1.5 mg/dL in symptomatic patients (positive likelihood ratio [LR+] 3.6). Elevated urobilinogen had a somewhat higher likelihood of detecting the presence of at least 1 elevated LFT in symptomatic patients (LR+ 3.9). Limitations of the study included a predominantly Hispanic patient population, which may limit generalizability of results. Authors also cited literature stating that urinary urobilinogen testing had potential for false-negative and false-positive results depending on diet, diurnal variation, and disease states of the patient.²

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What is the best approach to managing a depressed patient who has not responded to a selective serotonin reuptake inhibitor (SSRI)?

EVIDENCE-BASED ANSWER

Augmentation with a second-generation atypical antipsychotic, lithium, or thyroid hormone increases response rates in depression resistant to monotherapy with an SSRI (SOR: **A**, meta-analysis of RCTs). Switching to venlafaxine improves remission rates compared with switching to another SSRI (SOR: **A**, meta-analysis of RCTs). Adding cognitive behavioral therapy (CBT) to usual treatment including antidepressants increases response and remission rates of treatment-resistant depression compared with usual treatment alone (SOR: **B**, RCT).

A 2015 meta-analysis of 48 RCTs (N=6,654, 65% women, mean age 44 years) evaluated augmentation with a non-antidepressant medication in patients with treatment-resistant depression, defined as failure to achieve remission with at least 1 first-line antidepressant medication (mostly SSRIs).¹ The duration required to establish treatment resistance was not defined and the doses of augmentation agents were heterogeneous across studies and not specifically defined in the review. Response was defined as a 50% reduction in depression score on whichever scale was used for each individual study. The numbers of trials and patients that were pooled for each comparison were not reported.

Over 2 to 14 weeks, adjunctive aripiprazole and quetiapine increased response rate (odds ratio [OR] 1.9; 95% CI, 1.3–2.7 and OR 1.9; 95% CI, 1.4–3.1, respectively) compared with placebo. Lithium also improved response rates compared with placebo (OR 1.6; 95% CI, 1.1–2.6). Most trials evaluating lithium augmented tricyclic antidepressants as opposed to SSRIs. Response rates in patients receiving augmentation with varying doses of thyroid hormone were significantly better compared with placebo (OR 1.8; 95% CI, 1.1–3.6).¹

A 2008 meta-analysis of 4 placebo-controlled RCTs included 1,496 patients with SSRI-resistant depression

switching to either a different SSRI (paroxetine 20–30 mg, citalopram 20–60 mg, or sertraline 50–200 mg) or a non-SSRI antidepressant (venlafaxine 75–300 mg, mirtazapine 15–45 mg, or sustained-release bupropion 150–400 mg).² Remission of depression was assessed using the validated Hamilton Depression Scale (HAM-D), a validated scale with scores ranging from 0 to 54 (with <8 considered remission and >18 indicating severe depression).

Patients switched to the non-SSRI medications had improved remission rates compared with patients switched to another SSRI (4 trials, N=1,496; RR 1.3; 95% CI, 1.1–1.6). For individual agents, only venlafaxine versus switching to another SSRI improved remission (3 studies, n=not reported; RR 1.3; 95% CI, 1.0–1.7; number needed to treat=22).²

A 2014 RCT compared 12 to 18 sessions of CBT plus usual care with usual care alone in 469 patients (72% female, mean age 50 years) with treatment-resistant depression.³ Usual care was defined as treatment “deemed clinically appropriate by the general practitioner,” including medication. Treatment-resistant depression was defined as good adherence with an antidepressant for at least 6 weeks with Beck Depression Inventory (BDI) scores of 14 or more. The type of antidepressant used in the study population was mixed, with 61% taking SSRIs. Subgroup analysis comparing types of antidepressant was not performed, and dosing was not reported. The BDI is a validated scale with scores ranging from 0 to 63 (<10 indicating minimal depression and >30 indicating severe depression). Response was defined as at least 50% improvement in BDI score from baseline and remission was defined as a BDI score less than 10.

At 6 and 12 months, CBT plus usual care increased response (OR 3.3; 95% CI, 2.1–4.1) and also improved remission (OR 2.7; 95% CI, 1.8–4.1) compared with usual care alone.³

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Does obesity (body mass index ≥ 30 kg/m²) change effectiveness of contraceptives in women?

EVIDENCE-BASED ANSWER

There is no association between BMI and pregnancy rate in users of depot medroxyprogesterone, transdermal patch, intravaginal ring, intrauterine devices (IUD), and subdermal implants. The effect of body weight on oral contraceptives in general is unclear, although norethindrone acetate 1 mg/ethinyl estradiol 20 μ g may not work as well (SOR: **B**, systematic review of RCTs and observational studies and 2 cohort studies).

A 2013 Cochrane review of 9 reports of 13 trials (5 RCTs, 1 cohort, and 7 noncomparative trials) examined the effectiveness of hormonal contraceptives in preventing unplanned pregnancies in 49,712 women.¹ Exclusion criteria included specific health issues such as HIV, diabetes, or noncontraceptive hormone use. Contraceptives examined were combined oral contraceptives (OC), transdermal contraceptive patch, subdermal implants, depot medroxyprogesterone acetate, and progestin-only vaginal ring. Only 5 studies compared BMI classes.

In a post hoc analysis of an RCT (N=1,171), women taking norethindrone acetate 1.0 mg plus ethinyl estradiol 20 μ g with a BMI of 25 kg/m² or more had an increased risk of pregnancy versus women with a BMI of less than 25 kg/m² (risk ratio [RR] 2.5; 95% CI, 1.0–6.1). The 4 other RCTs examined combined OC (n=1,736), depot medroxyprogesterone acetate (n=1,787), subdermal implant (n=1,168), and transdermal contraceptive patch (n=3,319) and found no increase in pregnancy in women with elevated BMI versus normal BMI. Combined data analysis was not possible due to study heterogeneity related to type of contraceptive and different BMI cutoffs.¹

In the largest prospective cohort study from the above systematic review, failure rates were compared among normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25–29.9 kg/m²), and obese women (BMI ≥ 30 kg/m²) using IUDs (levonorgestrel or copper T380A IUD) over 3 years.² For women using an IUD (N=4,200), there were 6 pregnancies in normal weight women (n=1,584), 6 in overweight women

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(n=1,149), and 7 in obese women (n=1,467), signifying no correlation between BMI and pregnancy rates (*P* value not given).

A prospective cohort study (N=1,523) examined failure rates among OC pills (n=779), the patch (n=143), or vaginal ring (n=601) over 3 years in different BMI categories: BMI less than 25 kg/m², BMI 25 to 29.9 kg/m², BMI 30 to 39.9 kg/m², and BMI 40 kg/m² or more.³ Cumulative failure rates increased each year, but after 3 years, the probability of failure using the pill, patch, or vaginal ring was not statistically different among the BMI categories.

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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 ARMY MEDICAL DEPARTMENT, THE ARMY AT LARGE, OR THE DEPARTMENT OF DEFENSE.

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What are the best approaches to management of chronic scapholunate dissociation?

EVIDENCE-BASED ANSWER

The first step is staging of injuries by evaluation of the ligaments, alignment, reducibility of the carpal bones, and development of arthritis. Arthroscopic debridement and electrothermal shrinkage is associated with good outcomes for less severe injuries, whereas severe injuries are often treated with capsulodesis and tenodesis (SOR: **C**, systematic reviews of small case series).

A 2013 systematic review of 38 studies, primarily retrospective case series (N=1,091) published between 1970 and January 2012, covered 13 different treatment options for the management of scapholunate instability in the absence of arthritis.¹ Injuries were divided into 3 groups with different treatment recommendations for each group.

The first group, predynamic and dynamic instability with partial tears, was treated in 1 prospective case series (n=19) using arthroscopic debridement, which provided symptomatic improvement in 85% of patients at 2 years, while in a retrospective case series (n=16), arthroscopic electrothermal shrinkage was shown to improve symptoms in 80% to 90% of patients at 2 years. The second group, dynamic instability with complete tears, was treated in a prospective study (n=18) with dorsal capsulodesis. Patients in this group showed reduced pain scores, from an 8 to a 5 on a 10-point visual analog scale, in all 18 cases at 45 months (*P*<.005). In a separate prospective study (n=102) dynamic tenodesis was found to improve grip strength by two-thirds at 5 years. In the third group, static instability with complete tears, patients were treated with 3-ligament tenodesis. In a retrospective case series (n=38), this treatment option showed improvement in pain at a mean follow-up of 46 months; however, these patients showed 50% loss of flexion and extension and 33% loss of grip strength compared with the uninjured side.¹

In conclusion, the review emphasized that high level evidence was unavailable and that “prospective, randomized studies with validated outcome measures are needed to establish the efficacy of interventions on symptoms and function.”¹

In 2013, another systematic review defined the stages of scapholunate instability (1–6) and summarized the treatment options at each stage based on 61 observational studies involving an unknown number of patients.² There was overlap of several studies between this review and the one above.

Stages of injury are defined as stage 1–partial scapholunate interosseous ligament (SLIL) injury; stage 2–complete disruption of SLIL with repairable ligament; stage 3–complete disruption of SLIL with irreparable ligament but normal alignment; stage 4–complete disruption of SLIL with irreparable ligament and reducible rotary subluxation of scaphoid; stage 5–complete disruption of SLIL with irreducible malalignment and intact cartilage; and stage 6–chronic SLIL disruption with cartilage loss.

For individuals with stage 1 injury, excision of the scarred portion of the SLIL, arthroscopic debridement, and electrothermal shrinkage were evaluated in a retrospective case series in 2005 (n=16); 14 participants regained full range of motion and 78% grip strength at 19 months with this combined therapy. In patients with stage 2 injury, a retrospective case series (n=12) reported that direct ligament

repair was effective with excellent or good results in 8 patients, satisfactory in 2 patients, and poor in 2 patients. Direct repair in conjunction with capsulodesis showed good results at 1 year in a prospective case study (n=1), with the patient returning to work without pain or limitations.²

Most evidence in the review focused on stage 3 and 4 injuries; this included the largest case series (n=162) on 3-ligament tenodesis. This study found that 62% of patients had little to no pain at 4 years, dorsiflexion was 80%, flexion was 69%, and grip strength averaged 80%. A retrospective comparative study (n=29) looked at results for capsulodesis and tenodesis in stage 3 and 4 injuries. This study demonstrated postoperative grip strength of 91% and 87% and range of motion of 64% and 63% compared with the unaffected side for capsulodesis and tenodesis, respectively. Operative techniques for stage 5 and 6 injuries are based on expert opinion: Data have not been published for these treatments.²

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What is the differential diagnosis for an incidentally discovered adrenal mass?

EVIDENCE-BASED ANSWER

In patients with incidentally discovered adrenal masses on imaging and no history of malignancy or signs and symptoms of adrenal disease, the differential diagnosis includes nonsecreting adenomas (75%–85%), cortisol-secreting adenomas (9%), and a number of uncommon causes (<5% total) such as pheochromocytomas, aldosteronomas, adrenal cortical carcinomas, myelolipomas, cysts, hematomas, ganglioneuromas, and metastases (SOR: **C**, retrospective case series).

A 2008 US retrospective study determined the prevalence and nature of incidental adrenal masses identified by computed tomography (CT) in low-risk patients.¹ A search

of consecutive chest or abdominal CT reports from January 2000 to December 2003 for adrenal findings identified 3,307 patients. Medical records were reviewed and patients with inadequate follow-up or those considered high risk (clinical suspicion for a functional adrenal mass or patients with imaging demonstrating malignancy) were excluded. The remainder were defined as low risk by 2 independent radiologists who reviewed the CT reports.

Overall, the study included 973 low-risk patients (567 women and 406 men) with 1,049 adrenal masses. Specific diagnoses were reached in 921 adrenal lesions, as follows: 788 (75%) adenomas, 68 (6%) myelolipomas, 47 (4%) hematomas, 13 (1%) cysts, 3 (0.3%) pheochromocytomas, 1 (0.1%) macronodular hyperplasia, and 1 (0.1%) adrenal cortical neoplasm with unknown malignant potential. The remaining 128 lesions were presumed benign based on imaging or clinical follow-up. Most lesions (87%) were characterized with high-resolution imaging—72% of which were accurately diagnosed on initial CT. A key limitation of this study was the lack of histologic diagnosis in most cases (due to suspected benign nature).¹

An Italian, multicenter, retrospective survey evaluated adrenal masses detected incidentally during imaging workup for nonadrenal complaints across 26 referral centers between 1980 and 1995, using patient record review and detailed questionnaires.² For inclusion, the adrenal mass must have been characterized using high-resolution CT or magnetic resonance imaging. Exclusion criteria included severe or paroxysmal hypertension, hypokalemia (<3.5 mEq/L), and clinical signs of hypercortisolism or hyperandrogenism.

A total of 1,096 cases were collected—92 of which were excluded for lacking data. Of the 1,004 remaining (420 males, 584 females), hormonal investigation revealed that 85% of the masses were nonhypersecretory adenomas, 9.2% were associated with subclinical Cushing’s syndrome, 4.2% were pheochromocytomas, and 1.6% were aldosteronomas. Histologic data collected on 380 of the included patients who had undergone adrenalectomy showed 198 cortical adenomas (52%), 47 cortical carcinomas (12%), 42 pheochromocytomas (11%), 30 myelolipomas (8%), 20 cystic lesions (5%), 15 ganglioneuromas (4%), 7 metastases (2%), and 21 other

histological diagnoses (6%). A key limitation of this study was the possibility of laboratory and pathological differences in criteria for diagnosis among institutions.²

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In healthy adults, does routine vitamin supplementation reduce the incidence of respiratory infections?

EVIDENCE-BASED ANSWER

Vitamin C does not reduce incidence of the common cold in the general population, but appears to have a protective effect in strenuous athletes (SOR: **A**, meta-analysis of RCTs). Daily dosing of vitamin D, but not bolus dosing, reduces respiratory tract infections (RTIs) in the general population (SOR: **B**, meta-analysis of heterogeneous RCTs). Neither multivitamin nor vitamin E supplementation reduces the incidence of RTI in healthy older adults (SOR: **B**, single RCT).

A 2013 Cochrane review and meta-analysis of 29 RCTs (N=11,306) compared the incidence of the common cold, defined as any combination of upper respiratory symptoms with or without fever, in participants taking oral vitamin C supplementation (daily dose >0.2 g) or placebo.¹ A subset of 24 trials (n=10,708) included adults and children from the general community supplemented with 0.2 to 3 g vitamin C or placebo.

Vitamin C demonstrated no protective effect (relative risk [RR] 0.97; 95% CI, 0.94–1.0) compared with placebo. A subset of 5 RCTs (n=598) included participants exposed to strenuous exercise (marathon runners, competitive skiers, or soldiers) supplemented with 0.25 to 1.0 g/d vitamin C.

Follow-up ranged from 2 weeks to 5 years. In this subgroup, vitamin C supplementation demonstrated a 50% decreased incidence of the common cold compared with placebo (RR 0.48; 95% CI, 0.35–0.64).¹

A 2013 meta-analysis of 11 RCTs compared the incidence of upper and lower RTI in 5,660 patients 0 to 97 years old (mean age 16 years) taking oral vitamin D3 with both daily and bolus dosing at intervals (average dose 1,600 IU/d cholecalciferol) or placebo.² Follow-up ranged from 7 weeks to 3 years.

Overall, vitamin D supplementation was associated with a reduced risk of RTI versus placebo (11 trials; N=5,660; odds ratio [OR] 0.64; 95% CI, 0.49–0.84). Daily administration of vitamin D was also associated with a significant reduction in RTIs (7 trials, n=1,270; OR 0.51; 95% CI, 0.39–0.67) compared with placebo. Vitamin D administered in bolus doses once per month or less frequently was not associated with a reduction of RTIs (3 trials, n=382; OR 0.86; 95% CI, 0.62–1.2). The protective effect of vitamin D supplementation was not affected by health status, age, sex, trial duration, or baseline vitamin D levels. In order to account for heterogeneity, a random effects meta-analysis was used. The review was limited by significant heterogeneity among studies ($I^2=72%$), a reliance on relative measures of effect, and publication bias.²

A 2002 RCT (N=652) involving noninstitutionalized adults older than 60 years compared the incidence and severity of RTIs in patients orally supplemented with physiologic doses of multivitamins with minerals, 200 mg vitamin E, both, or placebo.³ Over a period of 15 months, patients reported symptoms of possible RTIs by telephone to a study nurse who determined whether they met the definition for RTI.

Compared with placebo, there was no decrease in RTI incidence or severity for multivitamins (RR 0.95; 95% CI, 0.75–1.2) or vitamin E (RR 1.1; 95% CI, 0.88–1.3).³

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What interventions are most effective for treating constipation in pregnancy or immediately postpartum?

EVIDENCE-BASED ANSWER

A daily fiber supplement increases the frequency of defecation and leads to softer stools in pregnant women (SOR: **A**, based on systematic review of RCTs). Stimulant laxatives are more effective than bulk-forming laxatives for treating constipation in pregnancy, but can cause uncomfortable side effects (SOR: **A**, based on systematic review of RCTs). Increased fluid intake is associated with less pregnancy-related constipation (SOR: **B**, based on a prospective cohort study). Taking a probiotic supplement during pregnancy is associated with increased stool frequency (SOR: **C**, case series).

A 2012 systematic review of 2 RCTs (N=160) examined the effectiveness of treatments for constipation in pregnancy.¹ The review included all randomized trials aimed at increasing the frequency or improving the caliber of stool during pregnancy, but excluded RCTs in which data were presented only in means.

In 1 of the 2 studies, a 10 g daily fiber supplement in the form of bran or wheat increased self-reported stool frequency (odds ratio [OR] of “no increased frequency of constipation” 0.18; 95% CI, 0.05–0.67) and led to self-reported softer stools in pregnant women (data not reported). In the second included study, stimulant laxatives were more effective than bulk-forming laxatives at resolving constipation (OR 0.30; 95% CI, 0.14–0.61) in pregnant women. However, stimulants laxatives were more likely to cause uncomfortable side effects such as abdominal pain (number needed to harm [NNH]=4) and diarrhea (NNH=6). Both bulk-forming and stimulant laxatives are pregnancy category C.¹

A 2014 systematic review aimed to evaluate the effectiveness of interventions including educational/behavioral methods, laxatives, and/or surgery to treat constipation during the postpartum period, and did not identify any RCTs that met inclusion criteria.²

A 2006 prospective cohort study evaluated the effectiveness of diet and exercise on bowel habits in 94 pregnant women during all 3 trimesters of pregnancy and the postpartum period.³ Seven-day food diaries, physical activity questionnaires, and bowel habit diaries were logged at 13 weeks’ gestation, 25 weeks’ gestation, 35 weeks’ gestation, and 6 weeks postpartum.

Functionally constipated mothers-to-be (exhibiting ≥ 2 symptoms from the Rome II diagnostic criteria) consumed significantly less water during the first trimester compared with their nonconstipated counterparts (1.9 vs 2.3 L/d; $P=.04$), more food in the second trimester (606 vs 476 g/d; $P=.04$), and less iron and food in the third trimester and postpartum periods (10.4 vs 13.3 mg/d; $P=0.02$; and 400.6 vs 472.0 g/d; $P=.04$, respectively).³

The authors concluded that higher water intake reduced the symptoms of constipation in the first trimester, but a further increase in water intake would be required to have the same effects in later trimesters and postpartum. No significant difference in bowel habits was identified when comparing light, moderate, and vigorous activity levels.³

A small, 4-week, uncontrolled intervention study performed in 2012 (N=20) evaluated the effect of a daily dose of a multispecies probiotic supplement, Ecologic® Relief (*Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *Lactobacillus casei*, *Lactobacillus plantarum*, and *Lactobacillus rhamnosus* (total 4×10^9 CFU) on defecation frequency in pregnant women older than 18 years and between 12 and 34 weeks’ gestation.⁴ Compared with baseline, at week 4 of the trial women taking the probiotic supplement reported increased frequency of bowel movements (3.1 to 6.7 per week; $P<.001$). No adverse effects were reported.

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Does massage therapy decrease pain or improve function in adults with low back pain?

EVIDENCE-BASED ANSWER

In adults with either subacute or chronic low back pain, massage therapy produces moderate short-term (≤ 6 months) improvements in pain and function; however, no benefit is seen beyond this time. In treatment of acute low back pain, massage therapy relieves pain only, and again only in short-term follow-up (SOR: **B**, systematic review of low-quality RCTs). In workers with either subacute or chronic low back pain, massage may be a useful adjunct to exercise therapy (SOR: **C**, based on expert opinion).

A 2014 Cochrane review evaluated 9 RCTs (N=1,105) comparing massage therapy with inactive controls for the treatment of low back pain.¹ Massage therapy was defined as soft tissue manipulation using the hands or a mechanical device, and inactive controls included waiting list, no treatment, sham therapy, and usual care (not described in detail). Low back pain duration was classified as acute (<4 weeks), subacute (4–12 weeks), or chronic (>12 weeks). Trials used a variety of validated pain and function instruments to measure outcomes. Due to the variety of measuring instruments, the reviewers reported pooled outcome data in terms of standardized mean differences (SMD). A SMD of 0.2 is considered small, 0.6 moderate, and 1.2 large.

In short-term follow-up (defined as immediately following treatment and up to 6 months afterwards), 7 studies (n=761) found massage therapy produced a moderate difference in subacute and chronic pain scores (SMD -0.75 ; 95% CI, -0.9 to -0.6). Six studies (n=725) with the same short-term follow-up found massage therapy also improved function (SMD -0.72 ; 95% CI, -1.1 to -0.39). However, at long-term follow-up (24–52 weeks), 3 studies (n=615) found massage therapy was ineffective in alleviating subacute and chronic back pain (SMD 0.02 ; 95% CI, -0.15 to 0.18) and made no difference in function (SMD -0.16 ; 95% CI, -0.32 to 0.01). Only 1 study (n=51) evaluated the effect of massage therapy on acute low back pain (defined as <4 weeks' duration). At a 1-week follow-up, massage therapy improved pain (SMD -1.2 ; 95% CI, -1.9 to -0.64) but not function (SMD -0.50 ; 95% CI, -1.1 to 0.06). Four studies (n=624)

reported on adverse events and found massage therapy to be associated with more adverse effects (most often an increase in pain) than inactive treatment (risk difference 0.06 ; 95% CI, 0 to -0.11 ; number needed to harm=17).¹

Overall, the studies were deemed low to very low quality. Limitations included small numbers of patients in some studies, as well as methodological errors such as high risk for selection bias, difficulty blinding patients and providers, high attrition rates, and imprecise measures of outcomes. The reviewers concluded massage was not effective treatment for low back pain of any duration beyond short term.¹

The American College of Occupational and Environmental Medicine (ACOEM) guideline on the evaluation and management of common health problems and functional recovery in workers found insufficient evidence to recommend massage therapy for treating acute low back pain.² For subacute and chronic low back pain, the ACOEM found limited evidence to support massage as an adjunct therapy to more effective treatments such as graded aerobic and strengthening exercises.

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What is the effect of electronic health records on malpractice claims?

EVIDENCE-BASED ANSWER

The use of electronic health records (EHRs) does not appear to effect the frequency of malpractice claims made or the frequency of malpractice claims paid (SOR: **C**, retrospective cohort and cross-sectional studies).

In 2013, a retrospective cohort study analyzed the effect of the use of office-based EHRs versus the lack of their use on malpractice claims in Colorado physicians.¹ A malpractice

claim was defined as any complaint requiring consultation with an attorney. Data were gathered from 894 office-based physicians insured through COPIC Insurance Company who responded to a survey, and COPIC Insurance company medical liability claim data (1982–2009).

The number of claims did not differ between physicians who used EHRs and those who did not (incidence rate ratio [IRR] 0.88; 95% CI, 0.52–1.46). For physicians who used EHRs the number of claims did not differ before and after EHR implementation (IRR 0.73; CI, 0.41–1.29). This study included physicians covered by a single malpractice insurer who were early adopters of EHRs.¹

In 2008, a cross-sectional study analyzed the effect of the use of EHRs in a medical office versus the lack of their use on paid malpractice claims.² Data were gathered using a random sample of 1,140 physicians in Massachusetts, and paid claims data from the Massachusetts Board of Registration in Medicine (BRM) data (1997–2007).

A smaller percentage of physicians using EHRs in a medical office had a history of a paid malpractice claim (6.1% vs 10.8%; unadjusted OR 0.54; 95% CI, 0.33–0.86), but when adjusted for sex, race, year of medical school graduation, specialty, and practice size, the relationship was no longer statistically significant (adjusted OR 0.69; 95% CI, 0.40–1.20). Data in this study were gathered solely on paid claims, and exclusively from Massachusetts physicians.²

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- 1 To become knowledgeable about evidence-based solutions to commonly encountered clinical problems.
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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

Do mineral supplements decrease the efficacy of quinolone antibiotics?

Bottom line

Mineral supplements and antacids containing the metal cations of iron, zinc, calcium, and aluminum appear to significantly lessen the bioavailability of quinolones, although the clinical significance on efficacy is not known (SOR: **C**, based on pharmacokinetic data).

Evidence summary

A 1989 4-way crossover study examined the effect of co-administering ferrous sulfate or a multivitamin with zinc on absorption of ciprofloxacin in 12 healthy volunteers.¹ The patients all received ciprofloxacin 500 mg once weekly for 4 weeks. During week 2, patients were randomized to receive either 325 mg iron 3 times daily or a daily multivitamin containing 23.9 mg zinc. During week 3, patients were crossed over to receive the alternative supplement; during week 4, they received no supplement.

The mean area under the concentration-time curve (AUC) was 14.46 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 15.71 $\mu\text{g}\cdot\text{h}/\text{mL}$ for weeks 1 and 4, respectively, which decreased to 5.37 $\mu\text{g}\cdot\text{h}/\text{mL}$ with ferrous sulfate and 11.29 $\mu\text{g}\cdot\text{h}/\text{mL}$ with the zinc multivitamin. This represented a decrease in bioavailability of 64% (95% CI, 39–81) with iron and 24% (95% CI, 2–50) with the zinc multivitamin.¹

A 1993 pharmacokinetic study examined the effect of chronic administration of calcium carbonate on the absorption of ciprofloxacin in 6 healthy young adult male volunteers.² In this 2-period, 2-treatment study, all subjects received ciprofloxacin 500 mg alone on day 1, then received 500 mg calcium 3 times daily on days 2 to 7.

The second dose of ciprofloxacin was administered on day 8. Ciprofloxacin levels were obtained throughout days 1 and 8.

AUCs were calculated for ciprofloxacin alone (mean 12.4 $\mu\text{g}\cdot\text{h}/\text{mL}$) and ciprofloxacin with calcium (mean 7.3 $\mu\text{g}\cdot\text{h}/\text{mL}$). Administration of calcium tablets with ciprofloxacin reduced its bioavailability by 43% (95% CI, 24–58).²

A 1992 3-way RCT examined the effect of co-administering 2 common antacids on the bioavailability of ciprofloxacin.³ Twelve healthy male volunteers were randomized to 750 mg ciprofloxacin alone, ciprofloxacin plus 3,400 mg calcium carbonate, or ciprofloxacin plus 1800 mg aluminum hydroxide.

The mean AUC for ciprofloxacin alone was 13.5 $\mu\text{g}\cdot\text{h}/\text{mL}$, ciprofloxacin + calcium was 7.82 $\mu\text{g}\cdot\text{h}/\text{mL}$, and ciprofloxacin + aluminum was 2.08 $\mu\text{g}\cdot\text{h}/\text{mL}$. Bioavailability was decreased by 40% with calcium and 85% with aluminum.³

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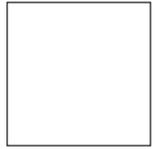
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What treatments are effective for relieving blepharospasm (eyelid twitching)?

EVIDENCE-BASED ANSWER

Botulinum neurotoxin type A (BoNT-A) is effective in up to 90% of patients with primary blepharospasm. IncobotulinumtoxinA (Xeomin®), a highly purified version of BoNT-A, results in small further improvements in blepharospasm and functional impairment in patients who have already received BoNT-A (SOR: **B**, RCTs). The addition of topical acetyl hexapeptide-8 (AH8) is not more effective than BoNT-A alone (SOR: **B**, RCT).

A 2011 double-blinded, RCT compared direct injection of Xeomin into the muscles of the eye with placebo injection in 109 patients with blepharospasm.¹ All patients treated with Xeomin had prior satisfactory response to 2 treatments with BoNT-A and had Jankovic Blepharospasm Rating Scale (JBRS) severity subscores of 2 or more, indicating moderate to severe intensity of symptoms. The JBRS score is used to characterize a patient's symptoms based on intensity and frequency, and is composed of 2 subscores: severity (0=none and 4=severe) and frequency of involuntary eyelid contractions (0=none and 4=functionally blind). Patients received either a single treatment with incobotulinumtoxinA (up to 50 U per eye) or placebo in a 2:1 ratio and followed up to 20 weeks. Treatment was defined as clinically relevant if there was at least a 0.8 point difference compared to placebo treatment.

At 6 weeks posttreatment, the mean JBRS severity subscore was measured by an independent rater and demonstrated improvement in the incobotulinumtoxinA group (mean difference [MD] 1.0; 95% CI, 0.5–1.4). To

measure functional disability, functional impairment ratings were quantified through use of the Blepharospasm Disability index (BDSI). The BDSI is a self-rating scale in which the patient scores his or her perceived functional impairment in the areas of 6 daily activity items using a 5-point scale. The scale ranges from 0 (no impairment) to 5 (no longer possible due to my illness). The mean BDSI rating decreased by 0.4 in the treatment group compared with a worsening of 0.11 in the placebo group (mean difference 0.5; 95% CI, 0.2–0.7). Adverse events were reported in 70.3% of treated patients versus 58.8% of placebo patients, most of mild intensity (no statistical analysis reported). Eyelid ptosis (18.9% vs 5.9%), dry eye (18.9% vs 11.8%), and dry mouth (14.9% vs 2.9%) occurred most frequently. Tolerability was rated good/very good by 91.9% of incobotulinumtoxinA vs 85.2% of placebo patients.¹

A small 2013 double-blinded RCT of 23 patients with primary blepharospasm investigated the safety and efficacy of topical 0.005% AH8 as an adjunct therapy in blepharospasm to extend the duration of BoNT-A.² Patients receiving BoNT-A therapy for 3 monthly intervals with no change in injection pattern were eligible for inclusion. Twelve patients were randomized to BoNT-A injection and twice-daily topical application of 0.005% AH8 and 11 patients were treated with injection and twice-daily application of a placebo cream. JBRS scores were recorded at least monthly until the primary endpoint of return to baseline was reached.

In the BoNT-A and AH8 group, 33% (4 of 12) of patients had a longer time to return to baseline appearance after injection (3.7 months) compared with the placebo group (3 months), but the result was not statistically significant. There were no reported significant adverse effects of treatment.²

A 2009 Cochrane review evaluated the treatment of blepharospasm with BoNT-A versus placebo.³ Studies were eligible for inclusion if they evaluated the efficacy of BoNT-A

for the treatment of blepharospasm, were randomized, and were placebo-controlled. There were few RCTs that met inclusion criteria. The few controlled trials identified were of short duration, enrolled small numbers of patients, and exhibited poor internal validity, so all 13 were ultimately excluded from systematic review.

However, all trials found BoNT-A superior to placebo—reporting that 90% of patients benefited. As a result, the reviewers endorsed BoNT-A as an effective and safe for treatment of blepharospasm.³

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In low-risk pregnancies, is maternal morbidity increased for births occurring in birthing centers compared with hospital births?

EVIDENCE-BASED ANSWER

The maternal morbidity rates in birthing centers are comparable to conventional hospital births for low-risk pregnancies. In addition, cesarean delivery and assisted vaginal delivery rates are less common in alternative birthing centers (SOR: **A**, meta-analysis of RCTs). The best data are from birthing centers within or adjacent to hospital labor wards.

A 2012 Cochrane review of 10 RCTs studied 11,795 nulliparous and multiparous women at low risk for obstetric complications who received care in alternative birth settings and conventional hospital settings.¹ Low risk was defined as term (38–40 weeks), singleton pregnancies in cephalic presentation without complications. The alternative birth settings included homelike bedrooms within or adjacent to the labor wards with the core staff consisting of midwives

with minimal input from physicians. No RCTs were found that examined freestanding birth centers. Maternal morbidity outcomes included the use of medical interventions, uterine rupture, intensive care unit admission, postpartum hemorrhage, and sepsis.

Delivery in an alternative birth setting decreased instrumental vaginal birth (8 trials, n=11,202; relative risk [RR] 0.89; 95% CI, 0.79–0.99) and episiotomy (8 trials, n=11,055; RR 0.83; 95% CI, 0.77–0.90) compared with a conventional hospital labor room. There was no mention if midwives were qualified to perform instrumental deliveries. Transfers to a conventional hospital were due to failure to progress in labor, fetal distress, desire for analgesia, or cesarean delivery. Cesarean birth rates were lower in alternative birth settings (9 trials, n=11,350; RR 0.88; 95% CI, 0.78–1.00). Postpartum hemorrhage rates were similar between birth settings (6 trials, n=10,712; RR 0.94; 95% CI, 0.82–1.08) as well as rates of serious maternal morbidity/mortality events (4 trials, n=6,334; RR 1.11; 95% CI, 0.23–5.36).¹

A 2011 prospective cohort study of 64,538 women compared birth outcomes in obstetric units staffed by physicians and midwives, freestanding midwifery centers staffed by only midwives, and midwifery centers alongside a hospital staffed by midwives with physician supervision.² Patients included women whose labor was attended by a midwife with term (≥ 37 weeks), singleton pregnancies, and no known medical or obstetric risk factors prior to onset of labor.

Rates of “normal births,” defined as a composite outcome of births without labor induction, epidural or spinal analgesia, general anesthesia, instrumental delivery, caesarean delivery, or episiotomy, were 83% at freestanding birth centers and 76% at birth centers alongside hospitals, compared with 58% in obstetric units (adjusted odds ratio [OR] 3.9; 95% CI, 3.2–4.7 and OR 2.5; 95% CI, 2.0–3.1, respectively). Maternal blood transfusion was decreased in freestanding and alongside birth centers (OR 0.48; CI, 0.32–0.73 and OR 0.75; CI, 0.55–1.0) compared with obstetric units. There were no consistent relationships between place of birth and rates of third- or fourth-degree lacerations.²

A 2003 prospective cohort study of 2,957 low-income nulliparous and multiparous women with and without history of cesarean delivery examined maternal morbidity in a freestanding birth center compared with traditional physician-led care.³ The birth center provided a homelike, low-tech environment, and the program was collaboratively

run by obstetricians and certified nurse midwives. Traditional physician-led care included 2 hospital-based and 7 private physician practices. Established protocols were used to determine perinatal risk and eligibility for care in the birth center. The protocols were not defined, but exclusion criteria included at least 2 prior cesarean sections, an undocumented uterine scar, chronic hypertension, and substance abuse in pregnancy.

Rates of major intrapartum morbidity (defined as cord prolapse, placenta abruption, severe preeclampsia, eclampsia, fourth-degree perineal laceration, cervical and sulcus laceration requiring repair, postpartum hemorrhage, shoulder dystocia, and uterine rupture) were similar in the freestanding birth center compared with traditional care (adjusted risk difference 0.8%; 95% CI, -2.4 to 4.0).³

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Are pregnancy support belts effective in treating pregnancy-associated lumbopelvic pain?

EVIDENCE-BASED ANSWER

Pregnancy support belts may decrease pelvic girdle and low back pain (SOR: **C**, systematic reviews of low-quality RCTs). Flexible belts and rigid belts are associated with reduced symphyseal pain and appear to be equivalent. Flexible belts may be better tolerated than rigid belts (SOR: **C**, single low-quality RCT without placebo control).

A 2015 systematic review evaluated multiple nonpharmacologic approaches to treating pregnancy-related pelvic girdle pain or low back pain, including 3 RCTs

on support belts (N=307) out of 34 studies included.¹ RCTs on physiotherapy treatments for pregnancy-related lumbopelvic pain were considered for inclusion; studies were excluded if they evaluated treatments not commercially available, if they did not report specific treatment results, or if the research design was other than an RCT or prospective cohort. Gestational age and parity varied and was not reported in the systematic review. Patient ethnicity data were not available. Heterogeneity among studies precluded performance of a meta-analysis for any of the interventions.

One RCT (n=105) demonstrated that use of the support belt plus patient education was more effective for reducing pain intensity (as measured using a 100-mm visual analog scale) than exercises plus education (mean difference -23 mm after 6 weeks; 95% CI, -15 to -30) or education alone (mean difference -41 mm after 6 weeks; 95% CI, -33 to -48). Numerical results were not reported for the other studies but the authors stated that flexible belts reduced low back pain (based on 1 RCT; n=115). Rigid belts plus exercise improved pain, but this combination was no more effective than exercise alone for symphysis pubis dysfunction (1 RCT; n=87).

A 2009 systematic review of 7 RCTs, 2 nonrandomized controlled trials, and 1 quasi-RCT investigated the effectiveness of pregnancy support belts in treating pelvic girdle pain or low back pain during pregnancy.² Two of the 3 studies in the review above were included in this review. The study populations were pregnant women with pelvic girdle pain or low back pain at varying gestational ages (N=1,909) from the United States, New Zealand, or Europe with most trials originating in Sweden. One nonrandomized trial (n=40) included a treatment group consisting of the pregnancy belt alone; in the remaining trials (n=1,869), pregnancy belts were used in conjunction with other interventions, including education, specific exercises, ergonomic advice, acupuncture, warmth, massage, and TENS units. Due to heterogeneity among studies with regard to types of belts used, positions in which the belts were worn, and accompanying interventions, the studies were not pooled and individual numerical results were not reported.

The authors stated evidence was insufficient to conclude that belt usage alone reduced pain, because of difficulty separating the effect of belts from other treatments.²

A 2015 randomized parallel trial compared flexible belts (n=10) with rigid belts (n=10) over 3 weeks in pregnant

women with symphysis pubis dysfunction in New Zealand.³ Patients were eligible for inclusion if they were pregnant, at least 18 years old, had pubic symphysis pain for at least 2 weeks, and tested positive on at least 2 of 3 clinical tests (reproduction of pain with palpation, modified Trendelenburg's test, or straight leg raise test). Mean age was 29 years and mean gestational age was 31 weeks. Disability was assessed using the Patient Specific Functional Scale score, a 0 to 10 scale with a 2-point difference considered the minimal clinically important change.

Functional scores decreased for both flexible and rigid belt groups (combined mean decrease 2.3 points; 95% CI, 1.2–3.5). No significant difference was noted in functional scores between rigid and flexible belts (mean difference –0.1 points; 95% CI, –2.5 to 2.3). Participants preferred the flexible belt, although hours per day of belt use was similar (mean for flexible belt 5.0 h vs mean for rigid belt 4.9 h; $P=.97$). No adverse events were reported, except for subjective discomfort with the rigid belt. Major limitations of this study included its being unblinded, from a single center, with a small sample size, and lacking a no-treatment group.³

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Is progesterone an effective treatment for threatened miscarriage in pregnant women?

EVIDENCE-BASED ANSWER

Either oral or vaginal progesterone supplementation may be effective for treating threatened miscarriage; however, most trials have used dydrogesterone, a medication that is not available in the United States (SOR: **B**, inconsistent findings from systematic reviews of low-quality RCTs, and single low-quality RCT).

A 2011 systematic review of 4 RCTs (N=421) examined the effectiveness of progesterone therapy to treat women with threatened miscarriage, defined as vaginal bleeding, with or without abdominal pain, while the cervix is closed and the fetus is viable.¹ The trials compared various durations of either oral or vaginal progesterone with placebo or no treatment. The primary outcome was miscarriage of embryo or fetus.

Progesterone decreased miscarriage compared with placebo or no treatment in the pooled analysis of these 4 trials (RR 0.53; 95% CI, 0.35–0.79; number needed to treat [NNT]=9). No difference was noted in harms, including preterm labor, congenital abnormalities, pregnancy-induced hypertension, or antepartum hemorrhage. Overall, study quality was limited by small size and poor methodological quality (selection bias, lack of intention-to-treat, and lack of blinding). Finally, the studies were each conducted in a single center outside of the United States, half of which used a drug not available in the United States (oral dydrogesterone); it is uncertain if these results can be generalized to the US population.¹

A 2012 systematic review of 5 RCTs (N=660) similarly examined the effectiveness of oral dydrogesterone therapy to treat women with threatened miscarriage.² This systematic review had less stringent inclusion criteria than the 2011 systematic review; ultrasound-confirmed fetal viability was not required. Therefore, this review included 3 unique studies and 2 overlapping studies to the 2011 review. Despite these differences, the results were nearly identical, showing that progesterone was effective in preventing miscarriage in women with threatened miscarriage (odds ratio [OR] 0.47;

TABLE

Results of RCTs of progesterone versus placebo or no treatment for threatened miscarriage (<20–23 weeks' gestation)

Trial year	No. of patients	Route and form of progesterone	Dose and frequency	Duration of intervention	Comparison	RR or OR (smaller value favors progesterone)	95% CI
2009 ^{1,2}	146	Oral dydrogesterone ^a	10 mg BID	From study enrollment to 7 days after bleeding ceased	No treatment	RR=0.70	0.37–1.32
2009 ^{1,2}	191	Oral dydrogesterone ^a	40 mg once, then 10 mg BID	From study enrollment to 16 weeks' gestation	No treatment	RR=0.44 ^b	0.24–0.82 ^b
2005 ²	154	Oral dydrogesterone ^a (plus bedrest and folic acid)	40 mg immediately, then 20 mg per day	Unclear (1 week, or until bleeding stopped)	Bedrest and folic acid alone	OR=0.27 ^b	0.07–0.99 ^b
2004 ¹	50	Vaginal progesterone gel	90 mg daily	5 days	Placebo	RR=0.50	0.17–1.45
1987 ¹	34	Vaginal progesterone gel	25 mg BID	From study enrollment to 14 days after bleeding ceased	Placebo	RR=0.33	0.01–7.65
1967 ²	153	Oral dydrogesterone ^a (plus bedrest)	40 mg in 12 h, then 20 mg TID until symptoms remitted, then 10 mg BID x 5 days, and 5 mg BID for > 7 days	Variable	Bedrest	OR=0.61	0.29–1.3
1967 ²	16	Oral dydrogesterone ^a	20–50 mg per day	6–15 days	Placebo	OR=0.2	0.01–4.91

BID=twice daily; CI=confidence interval; OR=odds ratio; RR=risk ratio; TID=3 times a day.

^aOral dydrogesterone is not available in the United States.

^bStatistically significant difference.

95% CI, 0.31–0.7) and no significant adverse effects related to treatment were noted. Data from both systematic reviews have been summarized (see **TABLE**).

A 2014 single-center, single-blinded RCT (N=60) examined the effectiveness of progesterone on treating threatened miscarriage in pregnant women with vaginal bleeding before 20 weeks of pregnancy.³ The intervention was 400 mg of vaginal progesterone suppository daily until the bleeding stopped (up to 7 doses); the control group received no treatment. The primary outcome was miscarriage rate.

No difference was noted in the rate of miscarriage in the progesterone group compared with the control group (20%

vs 33.3%; *P*=.243). No adverse effects related to treatment were noted in this study. The results were limited by small sample size and lack of blinding.³

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What are the benefits and risks of aspirin as primary prophylaxis for CAD events?

EVIDENCE-BASED ANSWER

Aspirin decreases the risk of nonfatal myocardial infarction (MI) by 6 per 1,000 patients over 10 years for patients at low cardiovascular (CV) risk and by 31 per 1,000 patients over 10 years for patients at high CV risk. Aspirin also decreases the risk of cardiovascular disease (CVD) events (a composite of CV death, MI, and stroke), but has no significant effect on stroke, CVD mortality, all-cause mortality, or composite of nonfatal and fatal MI and death due to coronary artery disease (CAD). Aspirin increases major gastrointestinal (GI) and extracranial bleeding events by 4 per 1,000 patients over 10 years for patients at low CV risk and 22 per 1,000 patients over 10 years for patients at high risk (SOR: **A**, meta-analyses of high-quality RCTs). The excess risk of any GI bleeding or perforation in aspirin users versus nonusers is about 5 per 1,000 patients per year but increases up to 20 per 1,000 patients per year in patients with GI risk factors (SOR: **B**, case-control study).

A 2011 meta-analysis of 9 RCTs evaluated a total of 100,038 patients 30 to 85 years old (39% men and 61% women) to determine the effectiveness of aspirin for primary prevention of CV events.¹ Aspirin doses ranged from 75 to 500 mg daily or every other day, and the mean duration of follow-up varied from 3.7 to 10 years.

Aspirin reduced the risk of nonfatal MI (odds ratio [OR] 0.81; 95% CI, 0.67–0.99) and total CVD events, which included CV death, MI, or stroke (OR 0.87; 95% CI, 0.80–0.93), but did not reduce CAD events (included nonfatal and fatal MI and death due to CAD), stroke, CV mortality, or all-cause mortality. Two of the trials included patients with diabetes. Individual participant data were not analyzed, and there was no analysis of adverse events.¹

A 2009 meta-analysis of 6 primary prevention RCTs (6 of the 9 trials from the above meta-analysis) with a total of 95,000 men and women aged 19 to 94 years without a history of occlusive coronary disease evaluated the effect of aspirin versus no aspirin on the risk of CVD.² The trials including patients with diabetes were not included in this

meta-analysis. Aspirin doses ranged from 75 to 500 mg daily or every other day, and the mean duration of follow-up varied from 3.7 to 10 years.

Aspirin versus nonaspirin led to a lower relative risk (RR) of nonfatal MI per year of 0.77 (95% CI, 0.69–0.86). Aspirin did not reduce all-cause CV mortality (RR 0.94; 95% CI, 0.88–1.0). Aspirin increased the risk of major GI and extracranial bleeding (RR 1.5; 95% CI, 1.3–1.8), which represented 4 (95% CI, 2–7) more major bleeding events in a 10-year period per 1,000 low CV risk patients and 22 (95% CI, 12–33) per 1,000 high-risk patients. Notably, most of the participants were not taking statin therapy.²

In 2012, the American College of Chest Physicians used data from the 2009 meta-analysis described above and the Framingham risk score to estimate the probability of nonfatal MI based on CV risk.³ They found that aspirin use in patients at low CV risk (<10% 10-year risk) would be associated with 6 fewer nonfatal MIs, and patients at high risk (>20% 10-year risk) would have 31 fewer MIs per 1,000 patients over 10 years.

In 2006, a case-control study using 2 large patient databases estimated the excess risk of upper GI complications (UGIC) including bleeding or perforation according to GI risk factors in aspirin users compared with nonaspirin users.⁴ An aspirin user was defined as a patient for whom data suggested an aspirin prescription at any dose within 3 months of the index date for the study.

The study used 2 databases, in the General Practice Research Database (GPRD) from the United Kingdom with more than 3 million patients and in the Base de Datos para la Investigacion Farmacoepidemiologica en Atencion Primaria (BIFAP) from Spain with more than 1 million patients, to determine the distribution of UGIC risk factors among aspirin users and nonusers. The prevalence of aspirin prescription was 4.6% in the GPRD and 3.4% in the BIFAP, and 95% of the aspirin in the GPRD and 59% in the BIFAP was for cardioprotection. Pertinent GI risk factors for UGIC were found to be male sex; increasing age; current or recent use of nonaspirin NSAIDs; and history of dyspepsia, peptic ulcer, or upper GI bleeding or perforation.

The authors performed a case-control study using cases of UGIC from the GPRD database matched to controls to calculate the excess risk of UGIC from aspirin use. The excess risk of UGIC for aspirin users overall was calculated to be 6 and 5 complications per 1,000 aspirin users per year in the GPRD and BIFAP, respectively. However, for patients at high

risk, such as men older than 70 with a history of peptic ulcer, the excess risk was estimated at 20 cases per 1,000 aspirin users per year.⁴

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Are Latino migrant farmworkers at an increased risk of depression compared to the general Latino population in the United States?

EVIDENCE-BASED ANSWER

The answer is unclear for all Latino farmworkers. However, immigrant farmworkers from Mexico have higher levels of depression than US-born farmworkers of Mexican ancestry (SOR: **C**, retrospective cohort study). Immigrant farmworkers are at a higher risk of experiencing psychological distress, having a high overall rate of depression, and have a higher rate of depression than the general population in the United States (SOR: **C**, cross-sectional studies).

No studies were found directly comparing depression levels between migrant farmworkers and the general US Latino population.

A 2012 retrospective cohort study (N=1,429) compared depressive symptoms of self-identified Hispanic immigrants and nonimmigrants using a 20-item version of the Center for Epidemiologic Studies Depression (CES-D) scale, a screening tool that identifies depressive symptomatology related to major or clinical depression.¹ A threshold of 16 or more out of a possible 60 points on the CES-D scale indicates risk for clinical depression.

Within the Mexican subgroup (foreign born n=380, US

born n=387), a greater proportion of Mexican immigrants met the threshold for depressive symptoms than US-born people of Mexican ancestry (22.1% vs 14.7%; *P*=.008). The interpretation of data was limited by the relatively long presence of the immigrant population in the United States (≥20 years) compared with a more typical migrant immigrant population, which suggests a higher level of assimilation, and the use of depression data from a study initially designed around atherosclerosis in a multiethnic population.¹

A 2015 cross-sectional study of Latino farmworkers in Nebraska (N=200) assessed stress and depression using the Migrant Farmworker Stress Inventory (MFWSI) and the CES-D scale.² MFWSI scores range from 0 to 156, with a score of 80 or more indicating a person may be at greater risk for anxiety, depression, or suicidal behavior.

In the studied population, 30.5% had stress levels putting them at greater risk for experiencing psychological difficulties, and almost half (48.5%) were depressed. Limitations included the presence of crew chiefs and other workers during survey administration, which may have affected workers' responses, and the inability to generalize the results beyond the geographic region from which participants were recruited.²

A 2000 cross-sectional study (N=45) assessed the prevalence of anxiety and depression among Mexican immigrant farmworkers in 9 camps in northwest Ohio/southwest Michigan using the anxiety scale of the Personality Assessment Inventory (PAI) to measure anxiety and the CES-D to measure depression.³ A score of 60 or more on the PAI represents potentially significant anxiety that could impair function.

Overall, 28.9% of participants met the threshold for significant anxiety, compared with an estimated 16% of the general population that would reach the same criteria. Also, 37.8% of participants reported clinically significant depressive symptoms, compared with an expected 18% of the general population.³

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Can music therapy improve social interaction and verbal communication in individuals with autism spectrum disorder?

EVIDENCE-BASED ANSWER

Music therapy may improve social interaction and communication compared with standard care (SOR: **B**, systematic review of small RCTs and additional small RCTs). When compared with social skills training, music therapy may improve eye gaze and joint attention (SOR: **C**, small RCT).

A 2014 Cochrane review (10 RCTs, N=165) examined the effects of music therapy intervention on social interaction and communication among children (3–12 years old) with autism spectrum disorders.¹ Interventions ranged from 5 days to 7 months, were delivered by a professional music therapist, and included improvisation, singing songs/vocalizations, and listening to recorded or live music. Social interaction and communication skills were measured using several validated scales, so results were reported as standardized mean differences (SMD), where 0.2 is considered small, 0.6 moderate, 1.2 large, and 2.0 very large.

Compared with placebo, music therapy improved social interaction within therapy sessions (1 RCT, n=10; SMD 1.1; 95% CI, 0.02–2.1) and outside therapy sessions (3 RCTs, n=57; SMD 0.71; 95% CI, 0.18–1.3). Music therapy improved nonverbal (3 RCTs, n=30; SMD 0.57; 95% CI, 0.29–0.85) and verbal communications (6 RCTs, n=139; SMD 0.33; 95% CI, 0.16–0.49) compared with placebo within the session. However, no differences were noted between groups for communication skills outside the therapeutic context (nonverbal communication, 3 RCTs, n=57; SMD 0.48; 95% CI, –0.02 to 0.98; generalized verbal communication skills, 2 RCTs, n=47; SMD 0.30; 95% CI, –0.28 to 0.89).¹

A 2014 nonblinded, RCT (N=17) compared a 5-week music therapy intervention and a nonmusic social skills group for changes in social skills of children (6–9 years old) with autism spectrum disorder.² The music therapy group was facilitated by a board-certified therapist while the nonmusic social skills group was facilitated by a board-certified educator. Social interaction was measured by the

Social Responsiveness Scale (SRS), where scores range from 65 to 240 (lower scores indicating higher functioning).

The music therapy group had a significantly lower SRS score at postintervention than at pre-intervention (94 vs 114; $P=.018$). No significant change was noted in SRS in the social skills group from pre-intervention to postintervention (92 vs 104; $P>.05$). The final session was video recorded and later observed to detect 7 different social interactions with peers and adults. Eye gaze and joint attention (looking where another person is looking) were significantly better in the intervention group (to a level of $P<.05$), but the problem of multiple comparisons was not addressed.²

A 2013 RCT (N=21) examined the effects of a 16-week music therapy intervention on social engagement abilities in children (aged 36–60 months) with severe autism spectrum disorder.³ Children were randomized into “in-home, family-centered” music therapy plus early childhood intervention or early childhood intervention only. The music therapy group was facilitated by an accredited music therapist. Social interaction was assessed by the Vineland Social-Emotional Early Childhood Scale, with a mean of 100 and a standard deviation of 15 (scores ≥ 85 indicate adequate skills) as well as the preschool version of the SRS. Communication was evaluated by the MacArthur-Bates Communicative Development Inventories, Words, and Gestures, where scoring is based on the number of words produced. Scores below the 10th percentile reflect a delayed productive vocabulary.

At postintervention, the music therapy group had better social interaction than the early childhood intervention only group for the Vineland Scale (mean change 22 vs 0.9; $P<.01$). However, no significant change was noted between the music therapy and early childhood intervention groups on the preschool SRS (–7.70 vs –1.4; $P=.34$) or the MacArthur-Bates Inventory (79 vs 59; $P=.55$).³

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Is influenza vaccination during pregnancy safe for the fetus?

EVIDENCE-BASED ANSWER

Influenza vaccination during pregnancy is not associated with an increased the risk of adverse outcomes to the fetus, such as stillbirth, low birth weight, or preterm birth, small-for-gestational age, or neonatal death (SOR: **A**, consistent good-quality cohort studies and 1 systematic review of cohort studies).

A 2012 systematic review (27 studies, N=660,000) explored the relationship between influenza vaccination and fetal death or preterm birth.¹ Heterogeneity among studies with respect to type of vaccine, timing of administration, and patient population precluded meta-analysis.

Three cohort studies in the review examined the risk of fetal death after the influenza vaccine was given and found no significant change in risk, regardless of trimester during which the vaccine was administered. Eight studies of early fetal death (<20 weeks) and 5 studies of late fetal death (≥20 weeks) demonstrated no increased risk in vaccinated versus unvaccinated women. Eighteen of 19 observational studies showed no significant increase in risk of preterm birth (<37 weeks) in vaccinated women.¹

A registry-based retrospective cohort study based in Denmark in 2010 compared incidence of fetal death in vaccinated women (n=7,062) versus unvaccinated women (n=47,523).² These Danish hospitals and clinics used an influenza vaccine with an adjuvant (not used in most influenza vaccines the United States). To enhance validity of the cohort, all women with singleton pregnancies in Denmark ending during the year of study were included, except for those who had a miscarriage prior to 6 weeks and those who received the vaccination before the onset of pregnancy. In addition, propensity scores using various confounding variables (such as age, parity, use of drugs, place of residence) were used to exclude women whose scores indicated outlying features compared with the rest of the cohort. Healthy women were vaccinated generally in the second and third trimester, while women with comorbidities (eg, pulmonary disease, diabetes, cardiovascular disease, obesity, depression) were more commonly vaccinated during the first trimester.

Exposure to the vaccine was associated with no increased risk of fetal death (adjusted hazard ratio [HR] 0.79; 95% CI, 0.53–1.160), even when the subgroup of women with comorbidities was analyzed. Analysis of secondary outcomes individually showed no significant change in spontaneous abortion and a decreased risk of stillbirth (adjusted HR 1.11; 95% CI, 0.71–1.73 and adjusted HR 0.44; 95% CI, 0.2–0.94, respectively).²

A separate published study by the same authors on the same Danish cohort investigated the relationship between influenza vaccination and fetal outcomes.³ There were no significant differences in major birth defects (odds ratio [OR] 1.21; 95% CI, 0.6–2.45), preterm birth (OR 1.32; 95% CI, 0.76–2.31), low birth weight (OR 0.83; 95% CI, 0.41–1.67), or small-for-gestational age infants (OR 0.79; 95% CI, 0.46–1.37) in women who received the vaccine during the first trimester. Pregnant patients who received vaccination during their second or third trimester had similar results.

In 2013, a multicenter cross-sectional study studied 30,448 women who gave birth in public hospitals in Argentina.⁴ As in the Danish study, propensity scores were calculated using various potential confounding variables in order to optimize comparability of both study groups. Women who received the influenza vaccine during pregnancy were compared with women who did not with respect to perinatal outcomes.

Vaccinated women had a lower risk of all of the 3 primary outcomes (low birth weight, preterm delivery, fetal and neonatal death), with the overall composite risk showing a significant difference (7.0% vs 9.3%; $P<.01$). A composite OR, adjusted for confounders, was calculated to be 0.80 (95% CI, 0.72–0.89). Secondary maternal outcomes were also compared, suggesting lower risk of hospital admission during pregnancy (7.5% vs 6.3%; $P<.002$) and first trimester hemorrhage (1.8% vs 1.2%; $P=.01$), but no significant difference in hemorrhage during second and third trimesters. The unadjusted data suggested that 83 women would need vaccination to prevent one hospitalization, and 166 would need vaccination to prevent 1 first trimester hemorrhage.⁴

A 2013 cross-sectional study conducted in Norway reviewed cases of 46,491 patients who were pregnant during the peak 3 months of the influenza pandemic in 2009.⁵ In this analysis using a proportional-hazards model, women who were vaccinated during the time frame studied showed a nonsignificant reduction in risk of fetal

death (defined as >12 completed weeks' gestation; HR 0.88; 95% CI, 0.66–1.17), compared with women who were not vaccinated during pregnancy.

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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

What are the health risks of using insulin in patients with type 2 diabetes?

EVIDENCE-BASED ANSWER

Despite its effectiveness in improving blood sugar control, high-intensity insulin use is associated with more episodes of hypoglycemia (SOR: **A**, systematic review of RCTs). Compared with sulfonylureas plus metformin, insulin plus metformin is associated an excess of 11 deaths per 1,000 person-years (SOR: **B**, retrospective cohort). The evidence is conflicting about an association between insulin use and colorectal cancer (no SOR given).

A 2012 meta-analysis of 67 RCTs (N=21,347) evaluated the relationship of overall, nocturnal, and severe hypoglycemia with intensity of insulin treatment in patients with type 2 diabetes.¹ RCTs that compared different insulins or insulin regimens were eligible for inclusion, and treatment was required to last between 12 and 52 weeks. Additionally, included studies had to report a predefined target of the fasting blood glucose level. Only insulin-based arms were considered; placebo and oral antidiabetic drugs arms were excluded.

The final HbA1C achieved (range of 6.5%–9.0%) had a weak inverse correlation with percent of patients with hypoglycemia—predicting only 1.7% of the variance in hypoglycemia (coefficient of determination [r^2] 0.017; $P=.001$)—but had a stronger inverse correlation with percent of patients with severe hypoglycemia (not defined), predicting 45% of the variance (r^2 0.45; $P=.0001$). The final HbA1C had a weak inverse correlation with episodes per patient per year of nocturnal hypoglycemia, predicting 7% of the variance in nocturnal hypoglycemia (r^2 0.07; $P=.0001$).¹

A 2014 retrospective cohort study compared insulin plus metformin with sulfonylureas plus metformin to assess the risk of myocardial infarction (MI), stroke, and death in patients with type 2 diabetes.² The study matched 14,616 patients from a cohort consisting of 2,948 patients on insulin added to metformin and 39,990 patients on sulfonylureas added to metformin. The primary composite outcome was all-cause mortality, acute MI, and stroke hospitalization. Outcomes were ascertained using The International Classification of

Diseases, Ninth Revision Clinical Modification (ICD-9-CM) discharge diagnosis. Median follow-up was 14 months.

There were 42.7 primary outcome events per 1,000 person-years in the insulin group compared with 32.8 in the sulfonylurea group (adjusted hazard ratio [aHR] 1.30; 95% CI, 1.1–1.6). No differences were noted in the rates of stroke or MI, but all-cause mortality was significantly more common in the insulin group than the sulfonylurea group (33.7 vs 22.7 events per 1,000 person-years; aHR 1.4; 95% CI, 1.2–1.8).²

A 2014 meta-analysis of 7 case-control and 5 cohort studies (N=491,384) evaluated the relationship between insulin use and the risk of colorectal cancer (CRC) in patients with type 2 diabetes.³ The type or dose of insulin was not mentioned for many of the studies. The included studies determined the risk of CRC using incidence rates, although 3 cohort studies used mortality ratio.

The risk of CRC was significantly associated with insulin use (RR 1.7; 95% CI, 1.3–2.3). However, when subgroup analyses were conducted by study type, no association was detected in the cohort groups (RR 1.3; 95% CI, 0.95–1.7), but a significant association was detected in the case-control groups (RR 2.2; 95% CI, 1.4–3.3).³

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DIVING FOR PURLs

I've got a feeling: Gestalt versus Wells for ruling out pulmonary embolus

Hendriksen JM, Lucassen WA, Erkens PM, et al. Ruling out pulmonary embolism in primary care: comparison of the diagnostic performance of "Gestalt" and the Well's rule. *Ann Fam Med.* 2016; 14(3):227–234.

This post hoc analysis was derived from a prospective diagnostic cohort study comparing the diagnostic performance of a provider's Gestalt probability of pulmonary embolus (PE) with the Well's score with a point-of-care qualitative (POC-Q) d-dimer in patients presenting to primary care offices with at least 1 symptom of PE. The Gestalt and the Well's score were performed by the

physician caring for the patient at the time of presentation. All patients also received a POC-Q d-dimer test.

Patients were analyzed by Gestalt probability of PE of <20%, 20%–80%, and >80%. The primary outcome was the presence or absence of venous thromboembolism on any diagnostic imaging over a 3-month follow-up. Secondary outcomes included sensitivity, specificity, and metrics derived from them.

Overall, 73 of 598 (12.2%) patients had a PE. A Gestalt probability <20% and a negative d-dimer resulted in a sensitivity of 97% and a specificity of 29% (positive likelihood ratio [LR+] 1.96; negative likelihood ratio [LR-] 0.11); the Well's rule ≤4 with a negative d-dimer were

similar, with a sensitivity of 95% and a specificity of 51% (LR+ 1.37; LR- 0.09).

When Gestalt and Well's were used without the d-dimer, the sensitivity fell to 90% and 71%, respectively. Overall, fewer people were sent for imaging when using the Well's score; however, no data were provided.

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

Bottom line: Using Gestalt, or clinical opinion, is a good first step in assessing an outpatient with symptoms possibly consistent with PE. However, a Well's score was as reliable as Gestalt when used with a d-dimer, particularly for stratifying low- and high-risk patients. Use of Gestalt or Well's score without a d-dimer was less useful.

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Fluticasone plus salmeterol in persistent stable asthma likely safe

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

This randomized, double-blind, multicenter trial compared inhaled fluticasone with salmeterol to fluticasone alone in 11,679 adolescent and adult patients with moderate to severe persistent asthma within the last year. Patients were given a stratified fluticasone dose (100, 250, or 500

mcg), based on their asthma medications and assessment of control, with salmeterol 50 mcg or placebo as a masked, inhaled, dry powdered inhaler twice daily for 26 weeks.

The primary safety outcome was a composite of serious asthma-related events, including death, intubation, and hospitalization. The primary efficacy outcome was the first serious asthma exacerbation in which patients needed systemic steroids or hospitalization.

For safety, 36 serious asthma-related events occurred in 34 patients in the fluticasone-salmeterol group compared with 38 such events in 33 patients in the fluticasone-only group, which was not statistically different (hazard ratio [HR] 1.03; 95% CI, 0.64–1.66). For efficacy, the fluticasone-salmeterol group patients were less likely to experience at least 1 severe asthma exacerbation than patients in the fluticasone-only group (8.2% vs 10%; HR 0.79; 95% CI, 0.70–0.89).

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

Bottom line: Clinicians have additional assurance of safety and efficacy when following current treatment guidelines to use long-acting beta-agonists in combination with inhaled glucocorticoids as recommended. It is unclear if this assurance can be applied to patients with unstable and severe asthma.

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