CME

Evidence-Based Practice

A Peer-Reviewed Publication of the Family Physicians Inquiries Network VOLUME 18 NUMBER 2 FEBRUARY 2015

FPIN
Family Physicians Inquiries Network

IN DEPTH

What is the best treatment for ankylosing spondylitis?

Evidence-based answer

Both tumor necrosis factor α (TNFα) blockers and NSAIDs have positive effects on ankylosing spondylitis patients' global assessment, pain, physical function, and morning stiffness (SOR: **A**, meta-analysis of RCTs). NSAIDs are recommended as first-line medications and TNFα blockers are recommended for patients with persistently high disease activity despite conventional therapy (SOR: **B**, evidence-based guidelines).

Evidence summary

In 2010, a meta-analysis of 13 RCTs compared clinical outcomes in patients with ankylosing spondylitis (N=2,478; mean age 41 years; mean duration of symptoms 11 years) taking either NSAIDs versus placebo or TNFα blockers versus placebo.[1]

The NSAIDs included piroxicam, meloxicam, etoricoxib, naproxen, ketoprofen, ximoprofen (not available in the United States), and celecoxib. The TNFα blockers included infliximab, etanercept, and adalimumab. The efficacy of each pharmacologic intervention was evaluated according 6 outcomes: pain, physical function, acute-phase reactants, patient global assessment, spinal mobility and morning stiffness (**TABLE 1**).[1]

Both TNFα blockers and NSAIDs had positive effects on patients' global assessment, pain, physical function, and morning stiffness. Neither TNFα blockers nor NSAIDs had any effect on spinal mobility.[1]

In a 2012 systematic review of 3 RCTs (N=817), TNFα blockers (infliximab, etanercept, and adalimumab) were directly compared with placebo and indirectly compared with each other.[2] The treatment outcomes were examined over a 24-week period using the Assessment in Ankylosing Spondylitis Response Criteria 20 (ASAS 20).

A response was defined as ≥20% absolute improvement or at least ≥10 units reduction in ≥3 of 4 domains: patient global assessment (0–100 VAS), pain (0–100 VAS), Bath Ankylosing Spondylitis Function Index (0–100), and Bath Ankylosing Spondylitis Disease Activity Index (0–100), and no worsening of ≥20% in the remaining domain.[2]

All TNFα blockers were superior to placebo, and infliximab demonstrated the highest probability of being the best treatment when indirectly compared with other TNFα blockers (**TABLE 2**).[2]

CONTINUED

TABLE 1

Clinical effects TNFα blockers vs placebo and NSAIDs vs placebo on patients with ankylosing spondylitis[1]

	TNFα blockers vs placebo			NSAIDs vs placebo		
Outcomes	Studies	Total N	Standard mean difference (95% CI)	Studies	Total N	Standard mean difference (95% CI)
Pain (VAS 1–100)	2	592	–0.9 (–1.1 to –0.73)	5	1,080	–1.1 (–1.6 to –0.58)
Physical function (BASFI VAS 0–10)	5	957	–0.73 (–0.86 to –0.59)	5	1,080	–0.54 (–0.67 to –0.42)
Acute-phase reactants (CRP and if absent ESR)	4	924	–0.56 (–0.70 to –0.42)	2	287	–0.09 (–0.34 to 0.16)
Global assessment (scale 1–5)	5	837	–1.4 (–1.7 to –1.2)	3	894	–0.90 (–1.3 to –0.54)
Spinal mobility (lumbar flexion in centimeters)	5	1,266	0.21 (–0.09 to 0.50)	4	785	0.14 (–0.01 to 0.29)
Morning stiffness (duration in minutes)	1	40	–1.0 (–1.7 to –0.37)	4	785	–0.44 (–0.72 to –0.17)

BASFI=Bath Ankylosing Spondylitis Functional Index; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; VAS=visual analog scale.

TABLE 2

Direct comparison of TNFα blockers with placebo and indirect comparison with each other in patients with ankylosing spondylitis[2]

Treatment	Comparison	Outcome measure	OR (95% CI)	Probability of best treatment	Overall rank
Infliximab	Placebo	ASAS 20 at 24 weeks	6.9 (3.7–14)	72%	1
Etanercept	Placebo	ASAS 20 at 24 weeks	5.0 (2.7–8.1)	15%	2
Adalimumab	Placebo	ASAS 20 at 24 weeks	4.5 (2.6–8.1)	13%	3
Etanercept	Adalimumab	BMTC	1.0 (0.50–2.2)	N/A	N/A
Etanercept	Infliximab	BMTC	1.5 (0.67–3.3)	N/A	N/A
Adalimumab	Infliximab	BMTC	1.5 (0.67–3.5)	N/A	N/A

ASAS 20=Assessment in Ankylosing Spondylitis Response Criteria of 20%; BMTC=Bayesian Mixed Treatment Comparison; N/A=not applicable; TNFα=tumor necrosis factor α.

Recommendations

The 2010 evidence-based update of the Assessments in Ankylosing Spondylitis International Society (ASAS)/European League against Rheumatism (EULAR) recommendations for the management of ankylosing spondylitis included the following points:

- NSAIDs are recommended as first-line drug treatment for patients with ankylosing spondylitis who have pain and stiffness (SOR 9.3).
- TNFα blockers should be given to patients with persistently high disease activity despite conventional treatments (SOR 9.4).
- There is no evidence to support the use of DMARD (disease-modifying antirheumatic drugs like sulfasalazine or methotrexate) for axial disease (SOR 9.4).[3]

The strength of recommendation scores were based on an 11-point numerical rating scale assigned by a group of 21 international experts, 2 patients, and 2 physiotherapists after systematic review of literature and existing recommendations.[3] EBP

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

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The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

EBP CME
Evidence-Based Practice (ISSN 1095-4120) is published monthly to family clinicians by the Family Physicians Inquiries Network, Inc. FPIN is a nonprofit 501(C)3 educational and research consortium.

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Editorial

My *vitacilina* study

There I was, plodding through the slimy tropical undergrowth near the ancient Mayan city of Tikal, your typical accidental tourist, free of the burdens of adequate sun protection, malarial prophylaxis, antidiarrheal medications, or any one of the many vaccines that would have been available at a travel clinic back home.

I was wearing an outfit that shouted tourist: straw hat, Hawaiian shirt, and flip-flops. I kept gazing up at the Mayan architecture towering up through the jungle canopy. The sight was awesome. Then my foot slipped on some mossy limestone and I cut my toe.

I looked down and swore. I had promised myself that I would wear closed shoes in this region. Now I had an open dirty wound and was miles from transport with no first aid kit. Well, there was nothing to be done but put pressure on it until the bleeding stopped and walk back to the little town where I had started my day.

In the central market, I noticed a white tent where a woman appeared to be selling pharmaceuticals along with postcards. In halting Spanish, I obtained a tube of *Ungüento Vitacilina*™, with 0.3% *sulfato de neomicina*. As I slathered the *ungüento* in my wound, hoping my toe would not fall off, I realized that I probably needed to learn more a bit more about tropical medicine and travel health.

As it turns out, we all need to learn more. In a recent review, researchers discovered that in the entire canon of literature on common tropical diseases, there was only 1 research paper about the first- or second-line treatment of half of such ailments.[1] This amazing lack of attention appears to stem from the fact that most researchers live in resource-rich countries and tend to study diseases of their local communities.[2]

Would it be so hard for the rich world to focus on tropical diseases just a bit more? It really could relieve a lot of suffering. To do my small part, I am happy to report that my toe did not become infected or fall off. Consider that 1 positive case study for *Ungüento Vitacilina*.

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Increased risk for pyloric stenosis with macrolides in newborns and with peripartum use

Lund M, Pasternak B, Davidsen RB, et al. Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis: nationwide cohort study. *BMJ*. 2014; 348:g1908.

This cohort study assessed the association between use of macrolide antibiotics in mothers and infants from pregnancy onset until 120 days after birth and infantile hypertrophic pyloric stenosis (IHPS). Nearly one million liveborn singleton births were identified between January 1, 1996, and December 31, 2006, from the Danish Civil Registration system. Of these, macrolide use occurred in 3.0% of mothers during pregnancy, 2.2% of mothers from birth until 120 days postpartum, and 0.6% of infants during the first 120 days of life.

During the study period, 880 infants developed IHPS (0.9 cases per 1,000 births). The corresponding relative risk for IHPS was 29.8 (95% CI, 16.4–54.1) for macrolide use in days 0 to 13 and 3.24 (95% CI, 1.20–8.74) for days 14 to 120.

The postnatal maternal use relative risk for IHPS was 3.49 (95% CI, 1.92–6.34) for days 0 to 13 and 0.70 (95% CI, 0.26–1.90) for days 14 to 120. The maternal use of macrolides during pregnancy relative risk was 1.02 (95% CI, 0.65–1.59) for weeks 0 to 27 and 1.77 (95% CI, 0.95–3.31) for weeks 28 to birth for IPHS.

Erythromycin was the most common macrolide used, followed by azithromycin and roxithromycin, respectively. However, route of administration and inpatient utilization was not available.

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

Bottom line: There is a significant risk of infantile hypertrophic pyloric stenosis with the use of macrolides in infants during the first 14 days of life. However, the prevalence of IHPS is low and the use of macrolides is infrequent in this population.

Review and Summary Author: Jennie Broders, PharmD, BCPS, UPMC St. Margaret FMR, Pittsburgh, PA

Additional information regarding the PURLs and Diving for PURLs series can be found at: www.fpin.org/purlsfaqs

Ondansetron for irritable bowel syndrome

Garsed K, Chernova J, Hastings M, et al. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. *Gut*. 2014; 63(10):1617–1625.

This randomized, double-blind, placebo-controlled crossover study compared ondansetron with placebo in 120 patients aged 18 to 75 years with irritable bowel syndrome with diarrhea (IBS-D) from clinics in the United Kingdom. The treatment lasted 5 weeks, and during the initial 3 weeks the participants were given either ondansetron 4 mg or placebo tablets to be self-titrated up to a maximum of 2 tablets 3 times a day, based on stool consistency. For the final 2 weeks the patients maintained a stable dose, followed by a 2- to 3-week washout period before the crossover.

The primary outcome of the study was assessed using the Bristol Stool form score (range 1–7, higher scores indicating more liquid-like stool) with secondary endpoints of pain perception, urgency of defecation, bloating, frequency of defecation per day, number of days per week with pain, urgency, or bloating; and IBS severity score.

Ondansetron resulted in an additional 0.9-point reduction in Bristol Stool form score compared with placebo (95% CI, –1.1 to –0.6; $P<.001$) with a median dose of 4 mg 3 times daily. Worse diarrhea at baseline correlated to a decreased effect of ondansetron on stool form scores. However, ondansetron use also resulted in a significant reduction in number of days per week with urgency (–1.1 days; 95% CI, –1.5 to –0.6; $P<.001$) or bloating (–0.7 days; 95% CI, –1.1 to –0.3; $P=.002$). Ondansetron use was also associated with a reduction in stool frequency (11%; 95% CI, 4–18; $P=.001$) and an increase in whole gut transit time (10 hours; 95% CI, 6–14; $P<.001$).

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

Bottom line: Unlike current treatment options for IBS with diarrhea which only reduce diarrhea frequency, ondansetron use also reduces bloating and urgency symptoms. Patients with milder disease will likely have the greatest benefit.

Review and Summary Authors: Jason M. Corbo, PharmD, BCPS, and Niladri Das, MD, UPMC St. Margaret, Pittsburgh, PA

Another agent for PCOS-associated infertility

Legro RS, Brzyski RG, Diamond MP, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med.* 2014; 371(2):119–129.

This double-blind RCT compared letrozole with clomiphene among 850 women with polycystic ovary syndrome (PCOS) and associated infertility. After regular menses or oral progesterone-induced bleeding, the women started on either clomiphene 50 mg daily or letrozole 2.5 mg daily for 5 days for a maximum of 5 cycles, with dose escalation occurring with the start of each cycle based on progesterone levels until a maximum daily dose was reached of either 150 mg clomiphene or 7.5 mg letrozole.

The primary outcome was live birth. Pregnancy loss and congenital anomalies were secondary outcomes.

Live births occurred in 103 of 374 women in the letrozole group and 72 of 376 women who took clomiphene (RR 1.44; 95% CI, 1.10–1.87). There were 4 major congenital anomalies in the letrozole group, compared with 1 in the clomiphene group (*P*=.65).

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

Bottom line: Letrozole is a promising treatment for PCOS-related infertility. The increased observed number of cases of congenital anomalies, however, is a concern that should be addressed in future studies before letrozole is widely recommended.

Review and Summary Author: Sandra Sauereisen, MD, UPMC St. Margaret FMRP, Pittsburgh, PA

Macrolides improve asthma

Reiter J, Demirel N, Mendy A, et al. Macrolides for the long-term management of asthma—a meta-analysis of randomized clinical trials. *Allergy.* 2013; 68(8):1040–1049.

This meta-analysis of 12 blinded, placebo-controlled RCTs compared prolonged use of macrolides (≥3 weeks) with placebo among 831 patients with stable asthma. There was no significant effect of macrolides on FEV1 (forced expiratory volume in 1 second), but a positive effect on peak expiratory flow was noted (weighted mean difference [WMD] 6.7 L/min; 95% CI, 1.4–12.1; *P*=.014).

The studies used different asthma symptom scores, but analysis demonstrated an improvement in the final score in the macrolide group (WMD –0.56; 95% CI, –0.73 to 0.39; *P*<.001). Macrolides were also associated with a small improvement in Asthma Quality of Life Questionnaire (AQLQ) score (range 1–7; WMD 0.18; 95% CI, 0.001–0.37; *P*=.048). Data were insufficient to evaluate the effect on asthma exacerbations or adverse effects, although nausea was more frequent in the macrolide treatment arms. No differences were found among the macrolides used (azithromycin, clarithromycin, roxithromycin, and troleandomycin).

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

Bottom line: Prolonged macrolide therapy led to very small improvements in asthma symptoms and AQLQ scores, which are of questionable clinical significance. EBP

Review and Summary Author: Gretchen Shelesky, MD, UPMC St. Margaret FMRP, Pittsburgh, PA

What is the safest treatment for constipation in children?

Bottom line

Many laxatives are used to treat childhood constipation, and it is unclear which treatment is safest because not all laxatives have been compared in head-to-head trials. Polyethylene glycol (PEG), often used as a first-line treatment, has been shown to be safe and more comfortable than enemas. PEG and lactulose have rates of adverse effects similar to placebo. PEG, Milk of Magnesia, and fiber mixtures all can cause dose-related diarrhea (SOR: **B**, based on RCTs and systemic reviews with consistent findings).

Evidence summary

A 2012 Cochrane review of 18 RCTs reported no serious adverse effects from osmotic or stimulant laxatives.[1] A 2-study meta-analysis of unpublished data (N=101) showed no statistically significant difference in serious adverse events between PEG and placebo (0% vs 8%; OR 0.17; 95% CI, 0.02–1.5). Minor adverse events were similar in both groups and included abdominal pain, diarrhea, flatulence, headache, and nausea, but the number of participants affected was not reported.

Studies comparing PEG with lactulose found no statistically significant difference in the proportion of patients who experienced at least 1 adverse event after receiving PEG or lactulose (24% vs 37%; OR 0.37; 95% CI, 0.14–1.03). Adverse events included diarrhea, abdominal pain, nausea, vomiting, and pruritus ani.[1]

An RCT comparing PEG with dioctyl sulfosuccinate sodium enemas for rectal fecal disimpaction in 90 children concluded that abdominal pain immediately after laxative administration was more frequent in the enema group than in the PEG group (82% vs 52%; *P*=.008).[2]

In a randomized, prospective comparison study of PEG 3350 without electrolytes and Milk of Magnesia in 79 children, one child was allergic to PEG 3350.[3] The only other significant adverse reaction was transient diarrhea in both groups, which improved with dose reduction (no incidence data reported). No statistically significant laboratory abnormalities were reported.

A separate RCT comparing PEG and Milk of Magnesia for constipation treatment in 94 children found that the percentage of patients with diarrhea was significantly higher in the Milk of Magnesia group than in the PEG group (28% vs 4%; *P*=.002).[4]

Finally, a randomized prospective comparison study of PEG 3350 with electrolytes versus a mixture of acacia fiber, psyllium fiber, and fructose (N=100) found that the only clinically significant adverse effect was transient diarrhea, which was reported in both groups and improved with dose reduction (no incidence data reported).[5] EBP

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What nonpharmacologic interventions are effective for reducing needle-related procedural pain in children and adolescents?

Evidence-Based Answer

Distraction techniques and hypnosis reduce needle-related pain among children and adolescents (SOR: **A**, meta-analysis of RCTs). Breathing exercises, cognitive-behavioral interventions, seated positioning, and stroking the skin before and during an immunization injection may also reduce pain (SOR: **B**, meta-analysis of low-quality RCTs).

A 2013 meta-analysis identified 39 RCTs (N=3,394) evaluating the efficacy of psychological interventions in managing needle-related pain in children 2 to 19 years old.[1] The needle-related procedures included venipuncture, intravenous (IV) line insertion, laceration repair, immunization, lumbar puncture, bone marrow aspiration, and allergy testing injections.

Because the studies used different self-reported pain scales, the meta-analysis reported results as standardized mean differences (SMD), which express the magnitude of effect in each study relative to the variability observed in that study. A SMD value of 0.4 to 0.7 indicates a moderate effect and >0.7 is considered a large effect.[1]

Two interventions were effective in reducing pain. Distraction with music, toys, books, cartoons, games, nonprocedural talk, or a combination of techniques reduced self-reported pain compared with standard treatment (19 trials, N=1,759; SMD –0.61; 95% CI, –0.91 to –0.32). Hypnosis, generally consisting of an initial session that was then repeated for the procedure, also reduced self-reported pain compared with standard treatment (5 trials, N=176; SMD –1.4; 95% CI, –2.3 to –0.48). The major limitations of these studies were unclear allocation concealment and randomization procedures and lack of blinding, which would have been difficult to achieve.[1]

A 2009 meta-analysis of 20 RCTs and quasi-RCTs (N=1,380) evaluated psychological techniques to minimize pain with childhood immunizations as measured by visual analog scales.[2] In children 3 to 7 years old, breathing exercises such as blowing bubbles or a party blower (2 trials, N=141; SMD –0.43; 95% CI, –0.76 to –0.09), child-directed distraction through videos, music, or stories (4 trials, N=263; SMD –0.28; 95% CI, –0.54 to –0.03), and cognitive-behavioral interventions such as instruction in relaxation and distraction techniques (3 trials, N=242; SMD –0.75; 95% CI, –1.0 to –0.48) were effective in reducing self-reported pain compared with no intervention. Most of the studies were rated as high risk of bias or unclear risk because of concerns with randomization, allocation concealment, and blinding.

Another 2009 meta-analysis of 19 RCTs and quasi-RCTs (N=2,814) evaluated various interventions for minimizing pain during childhood immunizations.[3] Of the nonpharmacologic interventions, 2 were effective.

One trial (N=108) assessed child-reported pain related to positioning in children instead of infants and found that children 4 to 6 years old in the seated position reported, on average, 1 point lower score on a 0 to 10 pain scale than those in the supine position (MD –1.0; 95% CI, –1.9 to –0.06). Another study (N=105) evaluating cutaneous stimulation found stroking the skin close to the injection site before and during the immunization versus no stroking decreased mean pain ratings by 1 point on a 0 to 5 scale (MD –1.0; 95%CI, –1.9 to –0.10). Both of these studies were also rated as high risk of bias due to inadequate or unclear reporting of randomization, allocation concealment, and blinding.

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Does depression and anxiety lead to overeating in children?

Evidence-Based Answer

Emotional eating and loss of control of eating among children and adolescents are associated with depression and anxiety, although it is unknown if there is a causal relationship (SOR: **B**, cross-sectional studies).

A 2010 cross-sectional cohort study looked at sleep-onset latency and its associations with emotional eating, depression symptoms, and anxiety.[1] Third and fourth grade students (N=356) were given the Sleep Habit survey, the Zung's Self-rating Anxiety Scale

questionnaire, a modified version of the Center for Epidemiological Studies Depression Scale (CES-D) survey, and the USA version of the Dutch Eating Behavior Questionnaire (DEBQ) for Children to measure emotional eating.

Multilevel regression analysis revealed significant direct relationships between sleep latency and emotional eating (*P*=.03), anxiety (*P*<.0001), and depression (*P*=.0017) (data presented graphically). The authors concluded sleep disturbance can lead to overweight and obesity due to emotional eating from emotional dysregulation.[1]

In 2010, a cohort analysis of 198 healthy girls in age cohorts of 11, 13, 15, and 17 years evaluated the effects of trait anxiety and depressive symptoms on obesity.[2] There were significant positive associations noted between depressive symptoms and body mass index (BMI) (*P*=.002; no data provided) when controlling for age and race. A 1 standard deviation increase in depressive symptoms was associated with a 0.84 unit BMI increase. However, after controlling for socioeconomic status, the association between depressive symptoms and fat distribution became nonsignificant. The authors linked psychological distress with a physiological measure of adiposity, with socioeconomic factors likely playing a role as well.

A 2009 longitudinal cohort study of 285 children (143 had major depressive disorder, 43 had anxiety, 99 healthy controls) with a median age of 12 years examined childhood anxiety, depression, and weight gain.[3] Psychiatric evaluations and BMI measurements were completed each year over 3 years after baseline measurements.

Depressed children had 7% higher BMI compared with the control group (*P*=.03), and anxious children had 12% higher BMI compared with the control group (*P*=.01).[3]

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What is the effect of oral vinegar ingestion on postprandial glucose levels?

Evidence-Based Answer

The evidence is mixed. Preprandial oral ingestion of vinegar may reduce postprandial glucose levels by anywhere from 19% to 25%. Any such effect may be greater in combination with high-glycemic index meals (SOR: **C**, RCTs with limited-quality disease-oriented evidence).

Before the advent of pharmacologic therapy for diabetes, vinegar consumption with meals was often used as a home remedy. Several small studies have investigated the effect of vinegar ingestion on postprandial glucose levels.

A 2010 randomized trial of 10 male patients (mean age of 32 years, BMI 24 kg/m^2) with type 1 diabetes (HbA1C 6.7%) compared the effects of preprandial ingestion of 30 mL vinegar with placebo on postprandial blood glucose levels.[1] The mean postprandial blood glucose (at 94 minutes) was higher in the control group than in the vinegar group (208 vs 154 mg/dL; *P*=.01).
In 2010, 4 randomized crossover trials (n=9–10 per trial) were conducted on separate adult subjects: the first 3 RCTs involved healthy adults, and the fourth involved adults with type 2 diabetes.[2] In the first trial, postprandial glucose level was measured after the ingestion of different doses of vinegar and high-glycemic index meals. A 0.5-g dose of acetic acid reduced the 2-hour postprandial glucose level by 23% compared with placebo (*P*=.05).

In the second trial, 1 g acetic acid was administered 2 minutes before the high-glycemic index meal and compared with vinegar administration 5 hours before the test meal and with placebo. Vinegar ingested 2 minutes before the high-glycemic index meal reduced the 2-hour postprandial glucose by 19%, which was not significant compared with placebo (*P*=.169); vinegar ingestion 5 hours prior showed no effect on the 2-hour postprandial glucose compared with placebo.[2]

In the third trial, the mean 2-hour postprandial glucose level was 90% greater with the vinegar treatment compared with placebo after the ingestion of a dextrose drink, although this difference was not significant (*P*=.059). In the fourth trial, involving patients with type 2 diabetes (4 men, 5 women, mean age 69 years), the ingestion of 1 g acetic acid before a high-glycemic

index meal reduced the 2-hour postprandial blood sugars by 15% compared with placebo, although this difference was not significant (P=.097).[2]

In a 2005 randomized crossover trial, healthy subjects (10 women, 1 man, mean age 28 years) consumed 20 g apple cider vinegar or placebo before meals with high-glycemic indices.[3] Vinegar ingestion (timing of ingestion with respect to meals not provided) reduced the 60-min glucose response to the higher glycemic meal by about 10 mg/L (P<.05, actual glucose values not provided).

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How accurate are blood glucose meters?

Evidence-Based Answer

At least 60% of blood glucose meters meet the 2003 guidelines of the International Organization for Standardization, which states that ≥95% of the time, glucose meters should be accurate ±15 mg/dL for readings <75 mg/dL and accurate to ±20% for readings ≥75 mg/dL. The American Diabetes Association (ADA) recommends patients using glucose meters receive regular evaluation of their sampling technique and results (SOR: **C**, expert opinion).

The International Organization for Standardization (ISO) sets guidelines that are used to investigate accuracy of glucose meters (see **TABLE** for the current standard, ISO 15197:2003, and a proposed standard, ISO 15197:2011).[1]

A cross-sectional study compared the accuracy of 19 different glucose meter models made by 12 manufacturers used by 28 patients with insulin-dependent diabetes (both type 1 and type 2) against a laboratory method to determine if they complied with ISO 15197:2003 and proposed ISO 15197:2011.[2] All were found to be compliant with the current standard, but only 8 of the 19 glucose meters were compliant with the proposed new standard. When the results were separated into blood glucose ranges of <100 mg/dL and >100 mg/dL, readings of 10 and 8 glucose meters, respectively, were compliant with the proposed standard. There was a wide range of overall accuracy (80%–99%).

TABLE

Minimum acceptable system accuracy criteria according to current and proposed ISO-Standard guidelines[1]

	Maximum deviation for reference glucose value	
ISO 15197:2003	At glucose levels <75 mg/dL ±15 mg/dL	At glucose levels ≥75 mg/dL ±20%
Proposed ISO 15197:2011	At glucose levels <100 mg/dL ±15 mg/dL	At glucose levels ≥100 mg/dL ±15%
At least 95% of the individual glucose results must fulfill these criteria.		

Another cross-sectional study of 100 patients with diabetes compared the accuracy of 27 glucose meter models made by 18 manufacturers to a reference laboratory method to see if they complied with ISO 15197:2003.[3] Sixteen of the 27 glucose meters were compliant. This study did not compare the glucose meters with the new proposed standard.

The most current "Standards of medical care in diabetes," published by the ADA in 2013, does not mention meter accuracy goals, but does mention that the appropriateness of a ±20% error is currently being reviewed by the FDA.[4] The ADA recommends patients using glucose meters receive regular evaluation of their sampling technique and results.

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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 Navy Medical Department, the US Navy at large, or the Department of Defense.

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Evidence-Based Practice learning objectives

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

Does counseling on or the distribution of devices for the safe storage of firearms increase their safe storage among firearm owners with children?

Evidence-Based Answer

Yes. Counseling and distribution of devices for safe storage of firearms improves safe storage and decreases gun presence in homes with children (SOR: **C**, heterogeneous prospective cohorts, unblinded and small RCT).

A systematic review of 6 prospective cohort trials and 1 RCT (N=3,376) using pre- and postintervention analysis compared the effectiveness of gun safety interventions: counseling (3 trials with adults), counseling and materials distribution (3 trials with children), and materials distribution alone (1 trial with adults).[1] Only 4 of the 7 trials (n=3,127) provided statistical measures of significance.

Of these, 1 cohort trial (N=112) in North Carolina found that counseling paired with safety pamphlets and gun-lock distribution led to increases in gun-lock usage and locked gun storage at 6-month follow-up, especially if children were in the home ($P<.05$, no data provided). Another cohort trial (N=103) in the rural Midwest showed that when parents of children presenting to an emergency department for mental health assessment were counseled about gun safety, gun safety practices (ie, gun locks/safes, removal of gun from the home) improved at 2-month follow-up ($P\leq.05$, no data provided). One other cohort trial (N=1,617) in an urban pediatric clinic showed that counseling during well-child checks alone led to no change in gun safety behavior at 1-year follow-up ($P=1$). The single RCT (N=1,295; with 311 gun owners) at an HMO in Washington state found that counseling and pamphlet distribution resulted in no between-group difference in removal of guns from the home at 3-month follow-up ($P=.72$). However, inclusion of a coupon for trigger locks in the intervention group led to a nonsignificant increase purchase of the trigger locks (8.0% vs 2.5%; $P=.06$). Given the heterogeneity of the study protocols and evaluation methods, the systematic review authors concluded further research was needed to determine the most effective interventions for improving gun-safety practices.[1]

A prospective cohort trial (N=151) examined the effectiveness of a gun-safety program implemented in an urban pediatric community health center serving mostly Hispanic patients in Arizona.[2] Families were assigned to either usual anticipatory guidance or a 1-time, pediatrician-administered gun safety intervention consisting of a 1- to 2-minute brief counseling session, distribution of brochures and free gun locks.

Families receiving the intervention, per self-report at 1 month, were more likely to have made an improvement in gun-safety practices, defined as use of a gun lock, gun safe, or separation of gun from ammunition (62% vs 27%; risk ratio [RR] 2.3; 95% CI, 1.5–3.4).[2]

Another prospective cohort trial (N=156; 41% homes with children) compared pre- and postintervention change in safe storage practices after an urban family medicine residency–based gun safety intervention in Texas.[3] Participants were assigned to a control, verbal, or verbal-plus-written counseling group regarding triple-safe gun storage (ie, locked, unloaded, child-access prevented). At baseline, 35% of all participants used triple-safe gun storage.

At 2- to 3-month follow-up, the intervention groups combined achieved greater triple-safe gun storage than control (44% in verbal and 51% in verbal-plus-written counseling vs 25% in control; $P=.035$). Further 2-group comparison showed that the intervention groups combined were more likely to have made at least 1 change toward safe gun storage compared with control (46% in verbal and 49% in verbal-plus-written counseling vs 29% in control; $P=.031$).[3]

A 2012 American Academy of Pediatrics (AAP) policy states that the safest home is one without guns.[4] The AAP urges all healthcare professionals to ask about the presence of guns in homes and to counsel parents to remove all guns from the home or restrict access to them. The AAP encourages gun lock and safe distribution. It supports regulations to prevent illegal sales to minors and a renewed ban on the sale of assault weapons to the general public.

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When should MRSA eradication be attempted for patient with colonization or infection?

Evidence-Based Answer

Hospitalized surgical and dialysis patients who are carriers of methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered for decolonization with mupirocin to prevent nosocomial *S aureus* infections (SOR: **A**, meta-analysis). However, studies specifically in patients with MRSA have not shown benefit (SOR: **B**, small RCTs). A focus on hygiene is recommended to prevent recurrent colonization and infection (SOR: **C**, expert opinion).

A 2011 Cochrane review of 8 RCTs (N=3,374) examined the use of mupirocin to prevent nosocomial infections in nasal carriers of *S aureus*.[1] The review included a heterogeneous group of patients in a hospital setting, most notably surgical and dialysis patients, and the length of treatment with mupirocin varied from 5 to 90 days.

Risk of nosocomial infections was significantly reduced in the mupirocin group compared with placebo or no treatment (8 trials, N=3,374; RR 0.55; 95% CI, 0.43–0.70). There was no clear risk reduction when patients were specifically MRSA carriers and treated with mupirocin compared with placebo (1 trial, N=98; RR 0.46; 95% CI, 0.12–1.6), although the confidence interval was wide.[1]

A 2008 Cochrane review of 6 RCTs examined the efficacy of antimicrobial agents for treating MRSA colonization.[2] These studies were heterogeneous in treatment regimens, definitions of colonization, and patient populations. All had small sample sizes. Treatment with topical nasal mupirocin did not decolonize the cultured nares, throat, or skin of patients (1 trial, N=98; RR 1.40; 95% CI, 0.64–3.0). Treatment with minocycline and rifampin systemically for 30 and 90 days likewise did not clearly result in decolonization (one 30-day trial, N=17; RR 9.5; 95% CI, 0.62–145; one 90-day trial, N=17; RR 3.5; 95% CI, 0.51–24) compared with placebo.

The Infectious Diseases Society of America's evidence-based recommendation states that little evidence is available on the effectiveness of eradication of MRSA for preventing recurrent infections in the community setting.[3] They recommend a focus on hygiene due to unclear evidence for eradication efforts to prevent recurrent colonization and infection.

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Does recreational running increase the risk of OA of the knee?

Evidence-Based Answer

No. Recreational running among adults does not increase the risk of osteoarthritis (OA) of the knee (SOR: **B**, cohort and case-control studies).

A prospective cohort trial asked 5,284 patients without knee or hip OA about their physical activity in 1986.[1] For each type of physical activity reported, an overall joint stress physical activity score (JSPAS) was created by multiplying a metabolic equivalent value for the activity, frequency per week, duration per session, and a joint stress weight. Three levels of physical activity were established using the JSPAS, with the lowest 25% identified as "low," the middle 50% as "moderate," and the upper 25% as "high." Three follow-up surveys of the participants were conducted over 13 years (1990, 1995, 1999). Knee or hip OA was identified by asking: "Has a doctor ever told you that you have osteoarthritis (hip or knee)?"

Increased JSPAS was not associated with an increased risk of hip or knee OA for either men or women. Knee OA for those with high JSPAS scores compared with those who were sedentary were not significantly different for either men (OR 1.3; 95% CI, 0.92–1.9) or women (OR 1.1; 95% CI, 0.47–2.4). No increase in the diagnosis of OA was found based on activity frequency, pace, or total weekly mileage.[1]

A prospective cohort study compared 45 long-distance runners (mean running time 214 min/week) with 53 age- and occupation-matched controls over 18 years with serial knee radiographs.[2] The radiographs were used to assign total knee scores (TKS; range 0–36)

based on 2 reader averages. The TKS was computed based on narrowing, sclerosis, and osteophytes in both the medial and lateral compartments of each knee.

Runners had worse TKS at baseline radiographs (1.3 vs 0.40; *P*=.018) but groups were similar at 18-year follow-up (3.6 vs 4.2; *P*=.60), suggesting more rapid progression among controls relative to runners. Although the difference was not statistically significant, severe OA findings (joint space width=0 mm on radiograph or presence of total knee replacement) at the end of the study were less common among runners than controls (2.2% vs 9.4%; *P*=.21), as were prevalent OA findings (osteophytes and/or joint space width <3 mm on radiograph) (20% vs 32%; *P*=.25).[2]

A case control study conducted in Finland compared men (n=55) and women (n=226) aged 55 to 75 years who required arthroplasty for OA to age- and sex-matched controls (n=524) selected randomly from the area.[3] Patients reported retrospectively about their participation in physical exercise. The risk of severe arthritis requiring arthroplasty among runners was not significantly higher for men (OR 0.26; 95% CI, 0.05–1.3) or women (OR 0.70; 95% CI, 0.48–1.0) compared with patients reporting no running.

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Are dietary interventions effective in the treatment of multiple sclerosis?

Evidence-Based Answer

Apparently no. Polyunsaturated fatty acid (PUFA) and vitamin D supplementation (along with interferon treatment) have not been shown to improve outcomes in patients with multiple sclerosis (MS) (SOR: **B**, systematic review of low-quality RCTs and small RCT).

A 2012 Cochrane review of 6 RCTs (N=794) compared PUFA supplementation versus a control monounsaturated fatty acid in different MS patient subtypes.[1] The interventions were the omega-3 fatty acid combination of eicosapentaenoic acid and docosahexaenoic acid or linoleic acid (an omega-6 fatty acid) versus the control, oleic acid (an omega-9 monounsaturated fatty acid). The Disability Status Scale (DSS) and the Kurtzke Expanded DSS (EDSS) were used to assess for the outcome of disease progression.

Compared with control at 24 months, PUFA supplementation demonstrated no benefit in any MS group: patients with MS in general (11–23 g/d linoleic acid; 2 trials, N=144; RR 1.0; 95% CI, 0.66–1.6); patients with progressive MS (2.9–3.4 g/d linoleic acid; 1 trial, N=65; RR 0.78; 95% CI, 0.43–1.4); or patients with relapsing-remitting MS (omega-3 combination at different doses; 1 trial, N=292; RR 0.82; 95% CI, 0.65–1.0). No studies on vitamin D supplementation met the minimal inclusion criteria. The RCTs were limited by a high dropout rate and inadequate descriptions of randomization, blinding, and adverse event reporting.[1]

A 2011 double-blind RCT conducted in Finland evaluated vitamin D_3 or placebo as adjunct therapy in 66 adults, aged 18 to 55, with MS concurrently on interferon β-1b.[2] Although the primary outcome was disease-oriented MRI changes, a secondary outcome was clinical disease progression as determined by the Expanded Disability Status Scale (EDSS).

While the reduction in total lesions on MRI was greater in the treatment group, total disease burden did not vary between the groups. Also, no differences were noted in risk of time to first relapse between the treatment and control group (HR 1.1; 95% CI, 0.41–3.1). The EDSS scores in the treatment group did not significantly decrease from baseline to 12 months (EDSS mean at baseline=2.0 vs 12 months=1.8; *P*=.071).[2]

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What is the best treatment for low HDL?

Evidence-Based Answer

No high-quality evidence is available regarding the impact of a low-fat diet for patients with low high-density lipoprotein (HDL). Moderate alcohol consumption may slightly increase HDL levels by less than 0.1 mmol/L. Medications including fibrates and HMG-CoA reductase inhibitors increase HDL by 3% to 10% (SOR: **C**, disease-oriented outcomes). In patients with both low HDL and low LDL with cardiovascular risk factors, pravastatin therapy reduces cardiovascular events by 4% over 6 years (SOR: **B**, RCT).

A 2011 Cochrane review of 3,544 publications evaluating the effect of a low-fat diet on low HDL levels found no publication that met their inclusion criteria.[1]

A 2011 systematic review (that included RCTs, crossover, and before-and-after trials) compared the effect of starting alcohol consumption with consuming water, fruit juice, or nonalcoholic drinks.[2] Patients who consumed moderate amounts of alcohol (up to 1 drink per day for women or 2 drinks per day for men) had an increase in HDL levels compared with the nonalcohol group (33 trials, N=764; mean difference [MD] 0.09 mmol/L; 95% CI, 0.05–0.12).

A 2010 systematic review and meta-analysis including 18 RCTs from 1950 to 2010 evaluated whether fibrate use in a heterogeneous patient population decreased cardiovascular endpoints compared with placebo.[3] Three of these trials reported results for change in HDL compared with placebo. Analysis of pooled results demonstrated an increase in HDL (MD 0.05 mmol/L; 95% CI, 0.01–0.10)

A 2004 placebo-controlled RCT of 2,073 patients (aged 31–75 years; average LDL ≤140 mg/dL and HDL ≤40 mg/dL; 93% men; 11% with diabetes; 43% with hypertension; 63% with prior myocardial infarction; 8% current tobacco users) compared the effects of pravastatin with placebo on coronary events.[4] Patients were given either pravastatin 40 mg or placebo once daily. Treatment with pravastatin increased HDL levels by 6% (P<.001). Over a median of 6.1 years, the absolute risk reduction in coronary head disease (CHD) death and nonfatal myocardial infarction was 4% and the NNT to prevent a major CHD event over 6 years was 25 patients (P=.008).

A 2007 substudy of an open-label randomized trial compared rosuvastatin 40 mg with atorvastatin 80 mg for their effect on HDL subpopulations.[5] The subgroup was composed of adult nonpregnant patients (n=306) who were included only after having adhered to a 6-week diet and exercise program. Patients were then followed at the end of 6 weeks of treatment with respective medication. The overall increase in HDL from baseline was higher in the rosuvastatin group than in the atorvastatin group (10% vs 3%; P<.0001). EBP

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What is the most effective therapy for childhood attention deficit hyperactivity disorder (ADHD)?

Bottom line

Osmotically released methylphenidate is slightly more effective than atomoxetine for treating the symptoms of ADHD, whereas immediate-release methylphenidate shows no benefit over atomoxetine (SOR: **B**, meta-analysis of RCTs with significant heterogeneity). Atomoxetine is more effective than placebo. The addition of clonidine extended-release (XR) in patients who had an inadequate response to stimulant medication monotherapy is also beneficial (SOR: **B**, RCTs).

Evidence summary

A 2011 meta-analysis of 9 RCTs compared the efficacy of methylphenidate (mean immediate-release dose equivalents of 0.8–1.1 mg/kg) with atomoxetine (1.3–1.6 mg/kg) in 2,762 children 6 to 16 years old diagnosed with ADHD.[1] No difference was found in the efficacy of methylphenidate versus atomoxetine on the ADHD Rating Scale-IV (ADHD-RS-IV; 18 items based on ADHD symptoms listed in the DSM-IV; total score ranges 0–54) during the 3- to 10-week follow-up (9 trials, N=2,762; standardized mean difference [SMD] 0.09; 95% CI, –0.08 to 0.26).

Osmotically released methylphenidate showed a statistically significant improvement in ADHD symptoms compared with atomoxetine (SMD 0.32; 95% CI, 0.12–0.53) while immediate-release methylphenidate showed no difference (SMD –0.04; 95% CI, –0.19 to 0.12). The authors noted significant heterogeneity among studies, primarily due to the inclusion of open-label trials.[1]

In a 2011 double-blind RCT, atomoxetine (0.5–1.8 mg/kg), provided in either a single daily dose or as a twice-daily divided dose, was compared with placebo for the treatment of 93 children aged 5 to 6 years diagnosed with ADHD.[2] Using the ADHD-RS-IV, evaluation by parents of the atomoxetine group at 8 weeks showed a statistically significant greater mean change compared with the placebo group (–13.2 vs –5.8; *P*=.009). Teacher ratings for the atomoxetine group also showed a statistically significant mean change compared with the placebo group (–12.5 vs –5.0; *P*=.02). The authors noted that decreases in the ADHD-RS-IV did not necessarily correlate with functional improvement.

Another 2011 RCT compared clonidine XR plus baseline stimulant medication with placebo plus baseline stimulant medication in 198 children and adolescents (aged 6–17 years) with hyperactive or combined subtype ADHD who had inadequate response to the stable stimulant medication.[3] The treatment consisted of 8 weeks of flexible dosing, 5 weeks of dose escalation (0.1–0.4 mg), and 3 weeks of dose tapering by 0.1 mg per week based on the patient's response to treatment. Patients were followed up at 5 weeks.

The clonidine XR plus baseline stimulant group had a greater improvement in the ADHD-RS-IV compared with the placebo plus baseline stimulant group (SMD –4.2; 95% CI, –7.8 to –1.1).[3] EBP

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GLOSSARY

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

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EVIDENCE-BASED PRACTICE

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1. When a patient asks you whether the ingestion of vinegar can help control postprandial blood sugar levels, your answer should be:
- ❑ a. There is no evidence to support the use of vinegar ingestion to control postprandial blood sugars
- ❑ b. Ingesting vinegar before a high glycemic index meal may lower postprandial blood sugar levels somewhat
- ❑ c. Vinegar ingestion is only effective if taken 5 hours before the meal
- ❑ d. Vinegar ingestion before a meal helps control postprandial blood sugars in meals of high glycemic index and low glycemic index

2. Which of the following statements is true based on the available evidence concerning eradication of *S aureus* in colonized individuals?
- ❑ a. The Infectious Diseases Society of America recommends MRSA eradication in carriers living in the community
- ❑ b. Mupirocin decolonization decreases infections in hospitalized surgical patients
- ❑ c. Mupirocin has a greater effect on MRSA than on MSSA colonization
- ❑ d. Renal dialysis patients should not undergo *S aureus* decontamination, due to increased risk of shunt infections by other organisms

3. Which of the following dietary supplementations has been demonstrated to slow the progression of multiple sclerosis and decrease episodes of relapse?
- ❑ a. Polyunsaturated fatty acids (PUFAs)
- ❑ b. Vitamin D_3
- ❑ c. A and B
- ❑ d. None of the above

4. All of the following statements are true about nonpharmacologic interventions for reducing needle-related procedural pain in children and adolescents *EXCEPT*:
- ❑ a. Cognitive-behavioral therapy is associated with less pain
- ❑ b. Lying down is associated with more pain than sitting up in 4- to 6-year-olds
- ❑ c. Distraction techniques are associated with more pain
- ❑ d. Hypnosis is effective for reducing pain with intravenous line insertion

5. A mother of a 15-year-old girl is concerned about her daughter's increasing weight gain and wonders if emotional distress can contribute to the increased weight gain. You can tell her:
- ❑ a. Emotional eating is not related to sleep habits and has no association with increased weight gain
- ❑ b. Current studies link anxiety and depression with increased body mass index (BMI) and body mass
- ❑ c. Current studies link only depression with elevated BMI in children
- ❑ d. There are no studies evaluating the issue of depression or anxiety with elevated BMI in children

6. Which statement about gun safety intervention is correct?
- ❑ a. The only American Academy of Pediatrics statement on gun safety recommends removal of guns from the home
- ❑ b. Counseling about safe gun storage by physicians (without provision of gun locks) has not improved safe storage of guns in any study
- ❑ c. Gun safety counseling and distribution of safety devices improves safe storage of guns
- ❑ d. Distribution of gun safety devices does not change safe storage practices

7. When a patient with type 2 diabetes checks a blood glucose level using a glucose monitor, according to industry standards (ISO 15197:2003), the results are supposed to be accurate within
- ❑ a. ±10% at all glucose levels
- ❑ b. ±20% at glucose levels ≥75 mg/dL
- ❑ c. ±15 mg/dL at all glucose levels
- ❑ d. ±15 mg/dL at glucose levels >75 mg/dL

8. Which of the following treatments may increase high-density lipoprotein (HDL) levels and improve cardiovascular outcomes in men with cardiovascular risk factors?
- ❑ a. Moderate alcohol consumption
- ❑ b. Low-fat diet
- ❑ c. A statin medication
- ❑ d. None of the above, no treatments appear to increase HDL

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Answer key: 1. b; 2. b; 3. d; 4. c; 5. b; 6. c; 7. b; 8. c

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- **Understand your responsibilities concerning scholarly faculty development**
- **Learn how to build faculty scholarly activity skills through journal clubs, writing projects, and online learning**
- **Strategize about faculty development opportunities for your faculty through FPIN's leadership network**

WHERE: **Sheraton Kansas City Hotel at Crown Center, Kansas City, MO**

PRESENTATION DATES AND TIMES: **Friday, March 27th at 2:30pm (RPS)**
Tuesday, March 31st at 9:45am (PDW)

FPIN
Family Physicians Inquiries Network

Evidence-Based Practice
ELECTRONIC VERSION • VOLUME 18 NUMBER 2 FEBRUARY 2015

Is it okay to use the nicotine patch during pregnancy?

Evidence-Based Answer

Evidence is conflicting on the efficacy and safety of nicotine replacement therapy (NRT) in pregnancy. Guidelines recommend against NRT until more evidence is available (SOR: **C**, expert opinion).

A 2012 Cochrane meta-analysis of 6 RCTs (N=1,745) examined the efficacy of smoking cessation treatments with NRT and behavioral support compared with placebo/control in pregnant women >13 weeks' gestational age and smoking at least 1 cigarette per day.[1] Nicotine replacement included patches, gum, and lozenges.

No statistically significant difference was noted in abstinence between the groups (6 trials, N=1,745; RR 1.3; 95% CI, 0.93–1.9). Among the secondary endpoints no statistically significant differences were noted in spontaneous abortion (3 trials, N=1,407; RR 1.2; 95% CI, 0.37–4.7) or stillbirth (3 trials, N=1,402; RR 2.0; 95% CI, 0.55–7.1). There were 8 stillbirths and 6 spontaneous abortions among 736 women taking NRT. The frequency of neonatal death (3 trials, N=1,386; RR 0.28; 95% CI, 0.06–1.4), preterm birth (4 trials, N=1,628; RR 0.85; 95% CI, 0.57–1.3), and neonatal intensive care unit admission (3 studies, N=1,386; RR 0.94; 95% CI, 0.64–1.4) were all similar between groups.[1]

A 2012 meta-analysis of 7 trials (RCT, quasi-RCT, and prospective observational trials, N=1,386) compared pharmacotherapy (nicotine patches, nicotine gum, or bupropion) with placebo in pregnant smokers.[2] A subgroup analysis of 4 trials in which 288 pregnant women used nicotine patches found a statistically significant effect for smoking cessation compared with placebo (RR 1.6; 95% CI, 1.1–2.4). Five studies described adverse effects from NRT to include skin irritation, headaches, dizziness, and nausea (no data provided). Three studies collected data on adverse neonatal effects, noting no statistical difference in low birth weight rates, mean gestational age, or preterm delivery.

The 2008 evidence-based guideline from the US Department of Health and Human Services could not conclude whether NRT during pregnancy is effective or safe and did not endorse the use of NRT until new evidence supporting safety was presented.[3] The guideline noted mixed findings in 4 trials evaluating safety in humans. Two of the studies (total of 280 pregnant women) showed no difference in safety. A third study was stopped due to safety concerns, but the safety issue was later attributed to a selection bias. The fourth study noting safety concerns was a retrospective cohort that the guideline authors believed had significant methodological weaknesses.

The guideline pointed out that while nicotine exposure from either NRT or cigarettes may cause adverse effects in the fetus, cigarette smoke exposes the fetus to additional chemicals. The guideline recommended behavior therapy as the first-line treatment for pregnant women who smoke.[3]

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1. Coleman T, et al. *Cochrane Database Syst Rev.* 2012; (9):CD010078. **[STEP 1]**
2. Myung S, et al. *BJOG.* 2012; 119(9):1029–39. **[STEP 1]**
3. Fiore MC, et al. *Treating Tobacco Use and Dependence: 2008 Update.* Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services. Public Health Service. May 2008. **[STEP 1]**

Which opioid is best for the management of labor pain?

Evidence-Based Answer

It is unclear which opioid is the most effective when given by patient-controlled analgesia (PCA): remifentanil may be more effective than fentanyl (SOR: **B**, single RCT) and nalbuphine may be more effective than meperidine (SOR: **B**, single RCT), yet remifentanil is equally effective as meperidine (SOR: **A**, meta-analysis). Given as needed intravenously (IV), butorphanol is more effective than either IV fentanyl or IV meperidine (SOR: **B**, single RCTs).

A 2012 meta-analysis of 12 RCTs (N=593) compared remifentanil via PCA (bolus doses ranging from 0.15 to 0.93 mcg/kg) with other analgesic techniques for management of labor pain.[1]

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One RCT compared remifentanil PCA (52 patients) with fentanyl PCA (54 patients). Remifentanil had a lower mean pain score (0–10 cm visual analog scale [VAS]) after 1 hour (mean difference [MD] –1.4 cm; 95% CI, –2.3 to –0.47). Oxygen desaturation occurred more frequently with remifentanil (risk ratio [RR] 1.3; 95% CI, 1.0–1.8) along with pruritus (RR 7.8; 95% CI, 1.0–60). No difference was found in nausea and vomiting, fetal heart rate abnormalities, or Apgar scores.[1]

Eight RCTs (n=417) compared remifentanil via PCA and pethidine (meperidine in the United States) via different routes: intramuscularly (IM), IV, or PCA. Remifentanil resulted in a lower mean pain scores after 1 hour on a 0–10 cm VAS in pooled data from all 8 studies (MD –2.2; 95% CI, –2.7 to –1.6) and a lower conversion rate to epidural analgesia (4 trials, N=246; 14 vs 43 events; RR 0.34; 95% CI, 0.2–0.58). Maternal satisfaction was higher with remifentanil in all 5 studies reporting this outcome, but results could not be pooled due to different rating scales. No differences were noted in maternal oxygen desaturation, pruritus, nausea, or vomiting. A limitation of this meta-analysis was the comparison between medications given by different routes.[1]

A 2010 Cochrane review of 57 RCTs investigated 29 comparisons between parenteral opioids for labor pain relief in low-risk term pregnancies.[2] In comparing remifentanil with meperidine, this review included only studies comparing the 2 drugs via the PCA route and found no significant difference in mean pain scores measured on a VAS (2 trials, N=122). However, fewer women receiving remifentanil required an epidural (RR 0.42; 95% CI, 0.20–0.89).

Three additional comparisons in this review are relevant as they show a significant difference between opioids that are available in the United States. In the nalbuphine PCA and meperidine PCA comparison, nalbuphine resulted in a lower mean pain score on a 6-point scale (1 trial, N=60; MD –0.51; 95% CI, –1.0 to 0.0). No difference was noted in maternal satisfaction, willingness to use the same method in the future, need for additional analgesia, nausea and vomiting, and Apgar score <7.[2]

Comparing butorphanol IV with meperidine IV, butorphanol resulted in a better pain relief score on a 5-point scale with higher scores indicating better pain relief (1 trial, N=100; MD 0.67; 95% CI, 0.25–1.1). Another trial (N=200) reported butorphanol resulted in less nausea and vomiting than meperidine (0/100 vs 12/100; RR 0.04; 95% CI, 0.00–0.67). No difference was noted in conversion to epidural, need for additional analgesia, assisted vaginal birth, cesarean delivery, and Apgar score ≤7.[2]

Comparing fentanyl IV and butorphanol IV, patients in the fentanyl group were more likely to request additional doses (1 trial, N=100; RR 1.4; 95% CI, 1.1–1.9) and request an epidural (RR 2.0; 95% CI, 1.0–4.0). No difference was noted in maternal drowsiness, cesarean delivery, Apgar <7, neonatal naloxone administration, need for neonatal ventilator support, or neonatal neurobehavioral scores.[2] EBP

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1. Schnabel A, et al. *Eur J Anaesthesiol*. 2012; 29(4):177–185. **[STEP 1]**
2. Ullman R, et al. *Cochrane Database Syst Rev*. 2010; (9):CD007396. **[STEP 1]**