

Evidence-Based Practice

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IN DEPTH

Signs and symptoms of mesenteric artery occlusion, and how you test for it

Evidence-based answer

Acute mesenteric occlusion (AMO) is characterized by severe abdominal pain “out of proportion” to physical examination, whereas chronic mesenteric occlusion (CMO) is characterized by postprandial abdominal pain that progresses over weeks to months (SOR: C, based on consensus and case-series data). No reliable serum markers exist for the detection of MO (SOR: B, based on observational studies with conflicting results). Contrast-enhanced multidetector computed tomography (MDCT) most reliably detects AMO (SOR: A, based on a systematic review). Sonography (US), CT, and magnetic resonance angiography (MRA) help diagnose CMO (SOR: C, based on consensus and case-series data).

Evidence summary

A retrospective study of 35 patients with a diagnosis of acute mesenteric ischemia reported that 86% of AMO patients were older than 50 years and 63% met at least 1 of the risk factors listed in the **TABLE**.¹ A retrospective study of 215 patients with a primary diagnosis of acute mesenteric ischemia found that patients presented to medical care an average of 12 hours (range, 2–200 hours) after the onset of symptoms. Abdominal pain was the “dominant” symptom. One-quarter of patients also presented with hypotension and one-third with signs of peritonitis (**TABLE**).² According to expert opinion,³ hypotension and signs of peritonitis are late, ominous findings.

The most extensive study on CMO is a 1997 review of 12 case series involving a total of 332 cases.⁴ The average age of presentation for CMO was 58 years, and the disease was more common among women and was associated with multiple vascular comorbidities. Abdominal pain was nearly ubiquitous, often postprandial, and associated with “food fear” and “small meal syndrome.” One-third of the patients presented with nausea, vomiting, or diarrhea, although constipation was also seen. On physical examination, weight loss was the most common sign, and an epigastric bruit was auscultated in most cases (see **TABLE**).⁴

A 2009 systematic review evaluated the diagnostic accuracy of serologic markers for intestinal ischemia, a condition that includes MO as a subset. In 20 observational studies involving a total of 978 patients, researchers found that no single test had sufficient sensitivity (sn) and specificity (sp)

TABLE

Diagnosing acute and chronic mesenteric artery occlusion

Mesenteric occlusion	Risk factors (% of patients with risk factor, if known)	Signs and symptoms (% of patients with sign or symptom)	Diagnostic modalities (sensitivity/specificity)
Acute	<ul style="list-style-type: none"> • Age >50 years (86%)^{1,11} • History of congestive heart failure, cardiac arrhythmias, recent myocardial infarction, hypovolemia, hypotension, sepsis, previous arterial emboli, vasculitis, deep vein thromboses, hypercoagulability, or chronic postprandial pain^{1,11} 	<ul style="list-style-type: none"> • Abdominal pain (100%)² • Severe abdominal pain out of proportion to physical examination¹¹ • Hypotension (26%)² • Signs of peritonitis (37%)² 	<ul style="list-style-type: none"> • Contrast-enhanced MDCT (93.3%/95.9%)⁶ • Mesenteric angiography (77%–100%/100%)⁷
Chronic	<ul style="list-style-type: none"> • History of smoking (75%)⁴ • Female sex (60%)⁴ • Peripheral vascular disease (55%)⁴ • Previous vascular surgery (52%)⁴ • Coronary artery disease (43%)⁴ • Hypertension (37%)⁴ • Previous abdominal surgery (35%)⁴ • Carotid artery disease (35%)⁴ • Chronic renal insufficiency (20%)⁴ • Diabetes mellitus (10%)⁴ 	<ul style="list-style-type: none"> • Abdominal pain (94%)⁴ • Postprandial abdominal pain (88%)⁴ • Weight loss (78%)⁴ <ul style="list-style-type: none"> • Epigastric bruit (63%)⁴ • Diarrhea (36%)⁴ • Nausea/vomiting (33%)⁴ • Constipation (18%)⁴ 	<ul style="list-style-type: none"> • Duplex ultrasound (89%/97%)⁸ • Color Doppler ultrasound (100%/87%–98%)⁹ • 3D magnetic resonance angiography (100%/87%)¹⁰ • Mesenteric angiography⁷

MDCT=multidetector computed tomography.

to establish or exclude the diagnosis of intestinal ischemia when compared with a reference standard of surgical or postmortem diagnosis.⁵ Of the markers studied, D-lactate (sn 85%, sp 48%), alpha glutathione S-transferase (sn 68%, sp 85%), and intestinal fatty-acid binding protein (sn 72%, sp 73%) performed better than tests such as elevations in serum lactate, amylase, arterial pH, and D-dimer.⁵

Contrast-enhanced MDCT is the emerging study of choice for AMO. A systematic review found 6 high-quality studies on the diagnostic accuracy of contrast-enhanced MDCT for AMO.⁶ In the accompanying meta-analysis of 619 cases, the overall disease prevalence was 23%. Pooled sensitivity was 93% (95% CI, 83%–98%) and pooled specificity was 96% (95% CI, 91%–98%).⁶

Selective mesenteric angiography has been considered the gold standard for AMO diagnosis. Its diagnostic accuracy varies, however, with a reported sensitivity of 77% to 100%.⁷ Of the 6 studies used to determine this sensitivity range, 5 studies involving a combined total of 249 patients reported sensitivities of 92% to 100%. A single study of 46 patients noted a sensitivity of 77% (misreported as 74% in Brandt et al).⁷

US has shown diagnostic accuracy for CMO. Using arteriography as the gold standard in 80 consecutive patients with symptomatic peripheral arterial occlusive disease (9 confirmed cases of CMO), fasting duplex US had a sensitivity of 89% and a specificity of 97% in predicting CMO of ≥70% stenosis.⁸ In a study of 82 nonconsecutive patients with suspected chronic intestinal ischemia or symptomatic peripheral vascular disease (12 confirmed cases of CMO in the celiac artery and 14 confirmed cases

in the superior mesenteric artery), color Doppler—when compared with angiography as the reference standard—had a sensitivity of 100% for predicting CMO in both arteries. Its specificity was 87% for the celiac artery and 98% for the superior mesenteric artery.⁹

Gadolinium-enhanced MRA was compared with a reference standard of angiography or surgery in a series of 14 consecutive patients who had undergone both MRA and correlative angiography/surgery for suspected chronic mesenteric ischemia (6 confirmed cases). For the diagnosis of CMO, MRA had a sensitivity of 100% and a specificity of 87%.¹⁰

EBP

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REFERENCES

1. Nonthasoot B, et al. *J Med Assoc Thai.* 2005;88(suppl 4):S46–S50.
2. Vokurka J, et al. *Hepatogastroenterology.* 2008;55(85):1349–1352.
3. Martinez JP, et al. *Emerg Med Clin North Am.* 2004;22(4):909–928.
4. Moawad J, et al. *Surg Clin North Am.* 1997;77(2):357–369.
5. Evennett NJ, et al. *World J Surg.* 2009;33(7):1374–1383.
6. Menke J. *Radiology.* 2010;256(1):93–101.
7. Brandt LJ, et al. *Gastroenterology.* 2000;118(5):954–968.
8. Gentile AT, et al. *Am J Surg.* 1995;169(5):476–479.
9. Lim HK, et al. *Radiology.* 1999;211(2):405–410.
10. Meaney JF, et al. *J Magn Reson Imaging.* 1997;7(1):171–176.
11. American Gastroenterological Association Medical Position Statement. *Gastroenterology.* 2000;118(5):951–953.

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A seasonal adjustment

Dear EBP Readers,

As many of you are aware, in my day job I work as a faculty member in a family medicine residency program, a job I have had for more than 20 years. One of the little rituals of the organization that I discovered soon after starting was the bestowing of the seasonal adjustment.

You see, the prior program director liked to engage in a bit of theatrics. About this time of year, he would always come into my office and solemnly close the door. He would sit down in the chair next to me, his face sad and serious, and say, "I'm sorry. The hospital did not make enough money for bonuses this year."

Maybe he thought I would be disappointed. But frankly, since the faculty shared all the work of the program equally, individual bonuses never made much sense.

But my boss was not done with the ritual. Next he would lean back in the chair, fold his hands behind his head, smile broadly, and say, "But we *did* get a seasonal adjustment." By some quirk of policy, the faculty salaries at the program were tied to the average faculty salaries in the area. If everybody else's salaries went up, ours would go up in lockstep. Nobody got rich, but at least we kept up with inflation. I believe that the director got great satisfaction from making sure the reward matched the work.

Well, we here at *Evidence-Based Practice* recognize that our readers also need to be rewarded adequately for *their* work, absorbing and integrating the information we present every month. Up until recently, EBP has conferred 3 hours of AAFP CME credit per issue. But now we're going to give you a seasonal adjustment. It gives me great satisfaction to say that each issue is now worth 4 AMA PRA Category 1 CME credits™.

Sure, we also recently increased the size of the Journal. But that's just what a seasonal adjustment is for—keeping up with inflation.

Regards,



Jon O. Neher, MD

How do we pick PURLs?

We scour sources that cover 500 journals daily for useful research evidence, and meet weekly to critically appraise and discuss studies that meet our criteria.

Here are our criteria:

Relevant: Is the topic relevant to family medicine?

Valid: Are the findings scientifically valid?

Change in practice: Would this change practice?

Medical care setting: Is this implementable in clinic, etc.?

Implementable: Can we implement this immediately?

Clinically meaningful: Are results clinically meaningful?

Topical NSAIDs are an option for acute musculoskeletal injuries

Topical NSAIDs for acute pain in adults. Massey T, Derry S, Moore RA, McQuay HJ. *Cochrane Database Syst Rev.* 2010;(6):CD007402.

This Cochrane review included 47 double-blind RCTs that studied more than 3,400 patients using topical nonsteroidal anti-inflammatory drugs (NSAIDs) for acute pain from musculoskeletal injuries. Overall number needed to treat (NNT) to achieve 50% pain relief for 1 week with all topical NSAIDs compared with placebo was 4.5 (range 3.9–5.3) over 6 to 14 days. Topical ketoprofen, ibuprofen, diclofenac, and piroxicam all had similar performance. Topical indomethacin performed somewhat worse (NNT=8); topical benzydamine was no better than placebo. No significant systemic adverse events occurred.

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

Bottom line: Topical NSAIDs are an alternative for treating acute musculoskeletal injuries. Lower systemic absorption may mean fewer adverse effects for patients who are sensitive to oral NSAIDs. However, only 1 topical NSAID, diclofenac, is available in the United States, by prescription only, at a cost of about \$64 for a 2-week course.

Article Reviewer: Nina Rogers, MD
Summary Author: Umang Sharma, MD

Intensive blood pressure control benefits some patients

Intensive blood-pressure control in hypertensive chronic kidney disease. Appel LJ, Wright JT Jr, Greene T, et al; for the AASK Collaborative Research Group. *N Engl J Med.* 2010;363(10):918–929.

This cohort study enrolled 1,093 African American patients aged 19 to 64 years with hypertensive chronic kidney disease (CKD), defined as a diastolic blood pressure (BP) >95 mmHg and glomerular filtration rate of 20 to 65 mL/min. Participants were originally in an RCT comparing intensive BP management (mean arterial pressure [MAP] <92 mmHg, or BP <125/75 mmHg) with standard BP management (MAP <107 mmHg or BP <140/80 mmHg). After completing the randomized portion of the trial, patients could elect to continue on in this cohort study, during which the BP goal for all participants was <130/80 mmHg. Patients were followed for 8 to 12 years.

No significant difference was noted in the combined endpoint of end-stage renal disease (ESRD, defined as need for dialysis or kidney transplant) or death between those originally in the intensive control group and those originally in the standard management group (hazard ratio 0.85; 95% CI, 0.71–1.02; $P=.08$). Post hoc analysis found a significantly lower incidence of the combined endpoint of ESRD or death in patients in the intensive arm who had baseline proteinuria (hazard ratio 0.67; 95% CI, 0.52–0.87; $P=.002$).

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

Bottom line: In this study, African American patients with hypertension, CKD, and proteinuria, but without other comorbidities such as diabetes mellitus, benefited from intensive BP management. Recommendations already exist to manage these patients intensively, so this finding is not practice-changing.

Article Reviewer: Mari Egan, MD
Summary Author: Umang Sharma, MD

Thigh-length stockings uncomfortable and show no patient-oriented benefit

Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial. CLOTS (Clots in Legs Or sTockings after Stroke) Trial Collaboration. *Ann Intern Med.* 2010;153(9):553-562.

This European RCT assigned 3,114 patients rendered immobile from a cerebrovascular accident (CVA) to either thigh-length or below-the-knee compression stocking for deep venous thrombosis (DVT) prophylaxis in the inpatient setting immediately after the CVA. Patients underwent a duplex ultrasound 7 to 10 days later.

Only combined asymptomatic or symptomatic proximal DVT at 7 to 10 days or 1 month was different between the 2 groups: occurring in 6.3% (98/1,552) of the thigh-length group and 8.8% (138/1,562) of the below-knee group ($P=.008$). The NNT with thigh-length stockings to prevent 1 DVT was 39.

Patients in the thigh-length group had significantly more total skin problems, which were mostly not severe (thigh-length group 9% [140/1,552], knee-length group 6.9% [108/1,562], $P=.03$, NNH with thigh-length stockings, 48). Patients were less likely to wear the thigh-length stockings due to discomfort.

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

Bottom line: Thigh-length stockings were not significantly better than knee-length stockings in any patient-oriented measure, and more patients experienced discomfort or adverse skin or limb effects with the thigh-length stockings.

Article Reviewer and Summary Author: Umang Sharma, MD

Inconclusive evidence that vapor rubs improve cough in kids

Vapor rub, petrolatum, and no treatment for children with nocturnal cough and cold symptoms. Paul IM, Beiler JS, King TS, Clapp ER, Vallati J, Berlin CM Jr. *Pediatrics.* 2010 Nov 8. [Epub ahead of print].

This RCT compared Vicks VapoRub (camphor, menthol, and eucalyptus oil in an ointment) with petrolatum ointment and no treatment in 138 children ages 2 to 11 years who had nocturnal cough and nasal and sleep symptoms caused by upper respiratory infection. Parents were instructed to massage the treatment into their child's neck and chest for a single night. Parents answered a validated 6-item survey before treatment and the morning after treatment.

Children's cough and sleep improved in the VapoRub group. The magnitude of the benefit was small (about 1 point on a 7-point Likert scale), but clinically meaningful. Despite the authors' efforts to blind parents to whether their children were receiving VapoRub or petrolatum, the parents (>85%) correctly guessed their children's treatment.

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

Bottom line: The masking of the placebo was not effective. This could undermine the validity of the results, because most parents knew if their children received VapoRub or petrolatum, and parents reported the outcomes. If the study were convincing, it would be a change in practice since such products are not currently recommended in standard sources. Nonetheless, we see no harm in using Vicks VapoRub. EBP

Article Reviewer and Summary Author: Debra Stulberg, MD

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What is the best initial antibiotic for patients hospitalized with MRSA cellulitis?

Bottom line

For patients hospitalized with methicillin-resistant *Staphylococcus aureus* (MRSA) cellulitis, vancomycin is likely as effective as newer antibiotics approved by the US Food and Drug Administration (FDA), such as linezolid, daptomycin, and tigecycline. (SOR: C, based on subanalysis or extrapolation of individual comparison RCTs.)

Review of the evidence

Cure rates for linezolid vs vancomycin were similar

A 2005 randomized, open-label, comparator-controlled study of 1,180 patients hospitalized with complicated skin and soft-tissue infections (cellulitis, abscesses, infected ulcers, or burns) and signs of systemic illness were given linezolid 600 mg IV or PO every 12 hours (592 patients) or vancomycin 1 g IV every 12 hours (588 patients). The intention-to-treat analysis showed 92.2% and 88.5% of the linezolid- and vancomycin-treated patients were clinically cured (defined as complete resolution of all preclinical signs and symptoms of infection) at 1 week after the end of treatment ($P=.057$). Of the enrolled patients, 47.6% were diagnosed with cellulitis. In this subgroup, 60.5% had MRSA and had a group cure rate of 91.6% in the linezolid group and 91.7% in the vancomycin group ($P>.999$).¹

Complete resolution occurred sooner with daptomycin vs vancomycin

In 2007, a prospective, open-label study compared daptomycin with vancomycin for the treatment of adult patients hospitalized with complicated skin and skin-structure infections. The trial assessed 53 patients treated with daptomycin 4 mg/kg every 24 hours IV and a matched cohort of 212 patients treated with vancomycin (dosed to achieve a trough of 5–20 mcg/mL). Positive MRSA cultures were more commonly found in the vancomycin group (75% vs 42%; $P<.001$). All patients achieved 100% clinical cure by the end of 14 days; however, patients treated with daptomycin achieved complete resolution 3 days earlier than patients treated with vancomycin (median 4 vs 7 days; $P<.001$).²

Cure rates for tigecycline vs vancomycin were similar

A 2008 randomized, double-blind, controlled trial compared tigecycline with vancomycin in 133 hospitalized adult patients with serious MRSA infections, of which 69.2% had complicated skin and skin-structure infections. Cure rates at the test-of-cure analysis (12–37 days after the last dose of antibiotic) were similar: 86.4% (51/59) for patients treated with tigecycline and 86.9% (20/23) for patients treated with vancomycin (no P value reported).³

Recommendation

According to the Infectious Diseases Society of America 2005 guidelines, “Linezolid, daptomycin, and vancomycin have excellent efficacy in skin and soft-tissue infections in general and against those due to MRSA specifically (based on at least 1 prospective randomized comparative trial). However, these agents should be reserved for patients who have severe infections requiring hospitalization or who have not responded to attempts to eradicate the infection.”⁴ The IDSA guidelines do not mention tigecycline, which received FDA approval after publication. EBP

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REFERENCES

1. Weigelt J, Itani K, Stevens D, Lau W, Dryden M, Knirsch C; Linezolid CSSTI Study Group. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. *Antimicrob Agents Chemother*. 2005; 49(6):2260–2266. [LOE 1b]
2. Davis SL, McKinnon PS, Hall LM, et al. Daptomycin versus vancomycin for complicated skin and skin structure infections: clinical and economic outcomes. *Pharmacotherapy*. 2007; 27(12):1611–1618. [LOE 2b]
3. Florescu I, Beuran M, Dimov R, et al. Efficacy and safety of tigecycline compared with vancomycin or linezolid for treatment of serious infections with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci: a Phase 3, multicentre, double-blind, randomized study. *J Antimicrob Chemother*. 2008; 62(suppl 1):i17–i28. [LOE 1b]
4. Stevens DL, Bisno AL, Chambers HF, et al; for the Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005; 41(10):1373–1406. [LOE 1a]

Evidence You Can Trust

The members of FPIN are deeply committed to providing accurate, unbiased, and evidence-based information that will help physicians provide better care to their patients—without the influence of industry support.

What is the best method for ablating the nail plate during surgical treatment of an ingrown toe nail?

Evidence-Based Answer

Partial or total nail avulsion followed by chemical matrixectomy with phenol is the preferred method for nail plate ablation for recurrence of ingrown toenails. (SOR: **A**, based on a systematic review.) However, sodium hydroxide ablation may have equal efficacy. (SOR: **B**, based on a single RCT.) Cryotherapy, CO₂ laser, and radio-wave ablation have less data but are acceptable alternative treatment options. (SOR: **C**, based on a single RCT, a retrospective case study, and a case series.)

A Cochrane meta-analysis of 9 trials (n=1,094 procedures) compared different treatment modalities for ingrown toenails. Procedures investigated included avulsion with and without phenol, excisional surgery with phenol, or excisional surgery alone. Primary outcomes were regrowth and relief of symptoms.¹

The use of phenol with a total or partial nail avulsion significantly reduced the rate of symptomatic recurrence (OR 0.07; 95% CI, 0.04–0.12) with greater patient satisfaction. Simple avulsion with phenolization was also more effective than an invasive surgical excision to prevent symptomatic recurrence after 6 months or more (OR 0.44; 95% CI, 0.24–0.80). However, phenol use was associated with an increased rate of postoperative infection, compared with not using phenol (OR 5.69; 95% CI, 1.93–16.8). Despite 1 trial having more than twice the number of patients than any other trial in this systematic review, sensitivity analysis was still statistically significant, with a 50% reduction in recurrence with simple avulsion and phenolization.¹

An RCT (n=19) compared cryotherapy with phenol ablation. A liquid nitrogen cryoprobe was placed on the germinal matrix for 20 seconds and repeated, whereas phenol (concentration not specified) was applied 3 times for 1 minute each. Outcomes were equal in healing (25.9 days for phenol and 27.1 days for liquid nitrogen), infection rates (no postoperative infections), and patient satisfaction (100% satisfaction).²

Another RCT (n=100) compared 80% phenol applied for 3 minutes with 10% sodium hydroxide applied for 20 seconds and repeated once. There were

no significant differences in pain or patient satisfaction. Regrowth at 1 year was not statistically different.³

A case series (n=73 procedures) using a radio-wave ablation technique with a frequency of 3.8 MHz applied for 2 to 4 seconds noted a 98.63% success rate (defined as no regrowth in 12 months) and subjective satisfaction in cosmetic and functional outcomes. Patients with minor presurgical infections took a prophylactic antibiotic prior to the therapy.⁴

A retrospective case study (n=154) using CO₂ laser therapy showed a 2.1% recurrence rate and an infection rate of 6.6%. Most patients (95.5%) reported mild to no pain.⁵

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The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Medical Department of the US Army or the US Army Service at large.

1. Rounding C, Bloomfield S. Surgical treatments for ingrowing toenails. *Cochrane Database Syst Rev*. 2005; (2):CD001541. [LOE 1a]
2. Blake A. A post-operative comparison of the nail avulsion using phenol and cryotherapy. *Br J Podiatry*. 2005; 8(4):128–132. [LOE 2a]
3. Cumming S, Stewart S, Harborne D, et al. A randomised controlled trial of phenol and sodium hydroxide in nail surgery. *Br J Podiatry*. 2005; 8(4):123–127. [LOE 1b]
4. Hettinger DF, Valinsky MS, Nuccio G, Lim R. Nail matrixectomies using radio wave technique. *J Am Podiatr Med Assoc*. 1991; 81(6):317–321. [LOE 2a]
5. Farley-Sakevich T, Grady JF, Zager E, Axe TM. Onychoplasty with carbon dioxide laser matrixectomy for treatment of ingrown toenails. *J Am Podiatr Med Assoc*. 2005; 95(2):175–179. [LOE 1b]

What's in an HDA?

We've asked Dr. Robert Gauer, author of numerous HDAs, What goes into writing an HDA?

I generally spend about 3 hours performing a literature search. When I get the articles I want, I go over their bibliographies and pull additional articles, spending about 8–10 hours of reading and processing.

From there, I am able to begin putting thoughts into words. This process takes about 4 hours; then I spend another 2 hours after I've let it sit for a few days. After the external peer review and a round or two of edits from Dr. Neher, it is usually ready for print.

My favorite part is the actual writing and seeing how I can take a mountain of information and make it into a molehill that still has relevance for the reader.

I can't tell you the countless times I have referred to an HDA for a question asked by a student or resident. We find the answer easily, and it takes less than 5 minutes to read.

Read more at: www.fpin.org/page/Gauer

What are the sensitivity and specificity of the PHQ-2 and the PHQ-9 in screening for depression?

Evidence-Based Answer

Validation studies of screening tools for major depression in primary care settings have demonstrated that the PHQ-9 has a sensitivity of 0.77 to 0.81 and the PHQ-2 has a sensitivity of 0.83 to 0.87. Specificity of PHQ-9 ranges from 0.91 to 0.94, while that of PHQ-2 ranges from 0.78 to 0.92. When depression is identified by the PHQ-2, completion of the full PHQ-9 or a clinical interview is recommended. (SOR: **A**, based on 2 systematic reviews of meta-analyses and other validation studies.)

The PHQ-2 consists of the first 2 items of the PHQ-9. The PHQ-2 scores range from 0 to 6, with a score of ≥ 3 being considered positive. A positive screen should be followed by completion of the PHQ-9 or a clinical interview to evaluate the presence of major depressive disorder.¹

Three studies to validate the PHQ-2 demonstrated some differences in the sensitivity and specificity values.² Both sensitivity (83%–87%) and specificity (78%–90%) of the PHQ-2 were high in the primary care setting. Lower sensitivity of the PHQ-2 (39%) was noted in a subspecialty practice (cardiology).

The PHQ-9 scores range from 0 to 27; consistent evidence has shown the optimal cutoff point is ≥ 10 .² The pooled specificity values of the PHQ-9 from various studies with about 15,000 patients were good (0.91–0.94) and the sensitivity values ranged from 0.77 to 0.81 in primary care practice and hospital specialty settings. One

meta-analysis³ of 4 validation studies of the PHQ-9 in the primary care setting with about 10,000 patients reported its sensitivity as 0.77 (95% CI, 0.71–0.84), while another meta-analysis² based on 7 validation studies in a similar primary care setting reported its sensitivity as 0.81 (95% CI, 0.72–0.88). The performance of the PHQ-9 is better in patient populations with a relatively high prevalence of a major depressive disorder.³ A wider variation in the sensitivity of the PHQ-9 in the hospital specialty setting was noted (95% CI, 0.64–0.88).

The key outcomes of these studies are summarized in the **TABLE**.

The PHQ-9 and PHQ-2 are the most commonly used self-administered tools for depression screening in different settings. These simple and reliable screening tools can be integrated in routine primary care practice. The US Preventive Services Task Force, however, recommends that routine screening for depression be administered only if there are systems in place to deliver adequate treatment and follow-up.²

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1. Kroenke K, Spitzer RL, Williams JB, Löwe B. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen Hosp Psychiatry*. 2010; 32(4):345–359. [LOE 1a]
2. Gilbody S, Richards D, Brealey S, Hewitt C. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. *J Gen Intern Med*. 2007; 22(11):1596–1602. [LOE 1a for PHQ-9 and 1b for PHQ-2]
3. Wittkampf KA, Naeije L, Schene AH, Huyser J, van Weert HC. Diagnostic accuracy of the mood module of the Patient Health Questionnaire: a systematic review. *Gen Hosp Psychiatry*. 2007; 29(5):388–395. [LOE 1a]

TABLE

Psychometric characteristics of PHQ-9 and PHQ-2

	Setting	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)
PHQ-9 (meta-analysis)				
14 studies ²	Primary care and hospital specialties	5,026	0.80 (0.71–0.87)	0.92 (0.88–0.95)
7 studies	Primary care and community		0.81 (0.72–0.88)	0.92 (0.83–0.93)
7 studies	Hospital specialties		0.78 (0.64–0.88)	0.91 (0.90–0.92)
4 studies ³	Primary care	10,000	0.77 (0.71–0.84)	0.94 (0.90–0.94)
PHQ-2 (original study)				
1 study ²	Primary care	580	0.83 (0.68–0.93)	0.90 (0.87–0.92)
1 study ²	General medical outpatients	520	0.87 (0.77–0.94)	0.78 (0.74–0.82)
1 study ²	Cardiology	1,024	0.39 (0.32–0.46)	0.92 (0.90–0.94)

PHQ=Patient Health Questionnaire.



What is the best treatment for erectile dysfunction (ED) in men with diabetes mellitus?

Evidence-Based Answer

In men with diabetes, phosphodiesterase type 5 (PDE-5) inhibitor therapy is superior to placebo in treating ED. (SOR: **A**, based on a systematic review and subsequent RCT.) It is unclear if one product is more effective than another. Prevention of worsening ED over time may be accomplished by lifestyle modification and improved blood glucose control. (SOR: **B**, based on a single RCT.)

A Cochrane review investigated 8 RCTs of 976 diabetic men treated with PDE-5 inhibitor therapy (sildenafil, vardenafil, or tadalafil) compared with 741 controls. Eighty percent of participants had type 2 diabetes, 20% had type 1. The mean age was approximately 50 years, the mean duration of ED was about 4 years, and the mean duration of diabetes mellitus was about 10 years. Outcomes were assessed using the International Index of Erectile Function (IIEF), a validated scale in which a score <10 indicates severe ED, >26 indicates no ED.¹

PDE-5 inhibitors were associated with an improvement in the IIEF scores (weighted mean difference [WMD] 6.6; 95% CI, 5.2–7.9). The WMD between percent of successful penetration attempts in the treatment and control groups was 27 (95% CI, 23–30).¹

A subsequent randomized, double-blind, placebo-controlled, multicenter trial of 298 men with diabetes and ED compared tadalafil with placebo. This study consisted of a 4-week treatment-free period followed by a 12-week treatment phase. Overall, 85% (254/298) of patients completed the study with compliance rates of more than 90%.²

Sexual function significantly improved when taking once-daily tadalafil 2.5 or 5 mg compared with placebo (mean changes in IIEF scores were 4.8 and 4.5 for tadalafil 2.5 and 5 mg, respectively, and 1.3 for placebo; $P < .005$ for both doses). Adverse events were similar in both groups except flushing, which was more frequent in the treatment group.²

In a recent RCT, 372 men were assigned to participate in an intensive lifestyle intervention (treatment) group or a diabetes support and education (control) group. The IIEF scores at 1 year in the

treatment group increased from 17.3 (± 7.6) to 18.6 (± 8.1), but remained stable in the control group. These results were similar when analyzed using intention-to-treat. For ED in the control group, 20% worsened, 57% were unchanged, 23% improved. In the treatment group, 8% worsened, 70% were unchanged, and 22% improved. Improvement differences were not significant, but a significantly smaller percentage of the treatment group than control group reported worsening ($P = .03$).³

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1. Vardi M, Nini A. Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus. *Cochrane Database Syst Rev.* 2007; (1):CD002187. [LOE 1a]
2. Hatzichristou D, Giamblasi M, Rubio-Aurioles E, et al. Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. *Diabet Med.* 2008; 25(2):138–146. [LOE 1b]
3. Wing RR, Rosen RC, Fava JL, et al. Effects of weight loss intervention on erectile dysfunction in older men with type 2 diabetes in the Look AHEAD trial. *J Sex Med.* 2010; 7(1 pt 1):156–165. [LOE 1b]

For patients with glucose intolerance, what medications reduce the risk of developing type 2 diabetes?

Evidence-Based Answer

Metformin (SOR: **A**, based on consistent RCTs) or acarbose (SOR: **B**, based on a single RCT) are likely to be effective for preventing or delaying the onset of diabetes compared with placebo. However, the most effective intervention remains lifestyle modification (SOR: **A**, based on a consistent RCT).

A multicenter RCT comparing acarbose 100 mg 3 times daily with placebo enrolled 1,429 patients aged 40 to 70 years with a body mass index (BMI) between 25 and 40 kg/m² and glucose intolerance. The risk of progression from glucose intolerance to a diagnosis of diabetes was reduced by 10% (ARR) over 3.3 years (NNT=10). Acarbose also significantly increased regression of glucose intolerance to normal glucose levels.¹

An RCT enrolled 3,234 adult patients with glucose intolerance and assigned them to placebo, metformin 850 mg twice daily, or lifestyle modification over a 4-year period. Patients included in the study were 25 years of age or older with a BMI of 24 kg/m² or

higher and a fasting plasma glucose concentration of 95 to 125 mg/dL and a glucose concentration of 140 to 199 mg/dL 2 hours after a 75-g glucose load. The average follow-up time was 2.8 years. The lifestyle intervention sought to achieve and maintain weight reduction of 7 lb through a healthy low-calorie, low-fat diet and included physical activity for at least 150 minutes per week. Patients assigned to this treatment group were enrolled in 16 lessons covering diet, exercise, and behavior modification to help them achieve their goals.²

Lifestyle intervention reduced the incidence of diabetes by 58% compared with placebo (AAR 14.5%; NNT=7). Metformin reduced the incidence of diabetes by 31% compared with placebo (AAR 7.2%; NNT=14). Lifestyle modification was significantly more effective than metformin ($P<.001$), supporting the hypothesis that type 2 diabetes can be prevented or delayed in patients at risk.²

A meta-analysis of 3 RCTs with 2,510 patients studied the use of metformin (either 250 mg 3 times daily or 850 mg twice daily) for the treatment of glucose intolerance. All studies had to provide follow-up information for 6 months or longer and list development of diabetes as an outcome. This meta-analysis included the metformin study discussed above. The authors calculated intention-to-treat outcomes using “worst case scenario” analysis (where all patient lost to follow-up in the treatment arm were presumed to develop diabetes and all patients lost to follow-up in the placebo arm were presumed to not develop diabetes). Patients with glucose intolerance treated with metformin for up to 3 years were less likely to progress to type 2 diabetes (OR 0.69; 95% CI, 0.58–0.82; NNT=14).³

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The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Medical Department of the US Army or the US Army Service at large.

1. Chiasson JL, Josse RG, Gomis R, et al. Acarbose for the prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002; 359(9323):2072–2077. [LOE 1b]
2. Knowler WC, Barrett-Connor E, Fowler SE, et al; for the Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346(6):393–403. [LOE 1b]
3. Lilly M, Godwin M. Treating prediabetes with metformin: systematic review and meta-analysis. *Can Fam Physician*. 2009; 55(4):363–369. [LOE 1a]

How effective are lower extremity compression devices for reducing DVT risk after a stroke?

Evidence-Based Answer

Evidence does not support the routine use of graduated compression stockings (GCS) to reduce the risk of deep vein thrombosis (DVT) after acute stroke. The occurrence of skin breaks, ulcers, blisters, and skin necrosis increases significantly in patients wearing GCS. No data support the routine use of intermittent compression devices to reduce the risk of DVT after acute stroke (SOR: **A**, based on RCTs).

In an outcome-blinded RCT, 2,518 patients with acute stroke were assigned to routine care plus thigh-length GCS or routine care without GCS. The primary outcome was the occurrence of DVT in the popliteal or femoral veins. A compression duplex scan was performed on all patients between days 7 and 10.¹

The primary outcome occurred in 126 (11.5%) patients allocated to thigh-length GCS and in 133 patients (11.7%) allocated to avoid GCS, a difference that was not significant (OR 0.98; 95% CI, 0.76–1.3; $P=.88$). However, there was a significant increase in the occurrence of skin breaks, ulcers, blisters, and skin necrosis in patients wearing GCS (64 [5%] vs 16 [1%]; OR 4.2; 95% CI, 2.4–7.3, NNH=26).¹

Another trial randomized 97 patients with acute stroke to routine care or routine care plus thigh-length GCS. The primary outcome was the occurrence of DVT in the popliteal or femoral veins. Color flow duplex ultrasound was used at baseline and again between days 7 and 10.²

DVT was detected in 7 of 65 patients allocated to stockings and in 7 of 32 controls (OR 0.43; 95% CI, 0.14–1.36). There was no discussion of potential complications of GCS in this study.²

A recent RCT compared the clinical effects of below-knee GCS and thigh-length GCS for DVT prophylaxis after stroke. This study randomly assigned 3,114 patients hospitalized with acute stroke to each therapy. The primary outcome was the occurrence of DVT in the popliteal or femoral veins. A compression duplex scan was performed between days 7 and 10.³

The primary outcome occurred in 98 patients (6.3%) who received thigh-length and 138 (8.8%) who received below-knee stockings, an absolute difference of 2.5 percentage points (95% CI, 0.7–4.4; $P=.008$).³

Currently, a third RCT is ongoing that is testing intermittent pneumatic compression versus avoidance of intermittent pneumatic compression in DVT prophylaxis after stroke. The results of this trial are expected to be published in 2014.

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1. CLOTS Trial Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet*. 2009; 373(9679):1958–1965. [LOE 1b]
2. Muir KW, Watt A, Baxter G, Grosset DG, Lees KR. Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke. *QJM*. 2000; 93(6):359–364. [LOE 1b]
3. CLOTS (Clots in Legs Or sTockings after Stroke) Trial Collaboration. Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial. *Ann Intern Med*. 2010; 153(9):553–562. [LOE 1b]

Is a D-dimer test useful in predicting future clot development after completion of vitamin K antagonist therapy for an unprovoked PE or DVT?

Evidenced-Based Answer

The use of a D-dimer assay 1 month after the conclusion of vitamin K antagonist (VKA) therapy for an unprovoked pulmonary embolism (PE) or deep vein thrombosis (DVT) is helpful in identifying individuals who may be at higher risk of having another venous thromboembolism (VTE). (SOR: **A**, based on multiple systematic reviews.) Clinically, however, the decision to continue or stop VKA therapy should also take into account the presence or absence of other sources of thromboembolic risk. (SOR: **C**, based on expert opinion.)

Due to the high rates of recurrence for VTE in individuals with VTE without a clearly identifiable cause (unprovoked DVT or PE), many clinicians and patients face uncertainty when deciding when to stop VKA therapy.

A multicenter, prospective cohort study was performed with 619 patients who had previously been on at least 3 months of VKA treatment for an unprovoked DVT or PE. One month after completion of VKA therapy, blood for a qualitative D-dimer test was drawn, and if normal, no further VKA therapy was given. Patients for whom the D-dimer test result was abnormal were then placed into 2 subgroups:

one receiving continued VKA therapy and one discontinuing all VKA therapy. Patients with congenital hypercoagulable states were not included.¹

Patients with an abnormal D-dimer test result 30 days after completion of VKA therapy who did not resume VKA therapy had a 15% recurrence rate of DVT/PE over as long as 18 months compared with a recurrence rate of only 6.2% in those with a normal D-dimer value who did not resume VKA therapy ($P=.005$).¹

A meta-analysis of 4 prospective cohort studies looked at 1,539 patients with VTE. Patients with an abnormal D-dimer test result at the end of VKA therapy were significantly more likely to have a VTE recurrence (16.6% recurrence rate over 18–36 months) than if they had a normal D-dimer value after cessation of VKA therapy (7.2% recurrence; odds ratio 2.36; 95% CI, 1.65–3.36). One limitation of this meta-analysis was the variable values used to define an abnormal D-dimer test result (between 250 and 500 ng/mL).²

In another meta-analysis of 7 RCTs and prospective cohort studies including 1,888 patients with an unprovoked VTE, researchers similarly found that individuals who appropriately stopped their initial VKA therapy and 1 month later had an abnormal D-dimer test result (abnormal defined as between 250 and 500 ng/mL) had an annual recurrent VTE risk of 8.9% versus a risk of only 3.5% ($P<.005$) for patients with a normal D-dimer value at the same posttreatment interval.³

All studies noted that other factors seemed to contribute to increased risk of recurrent VTE, such as increasing age of the patient, male sex, and the presence of an inherited bleeding disorder.⁴

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The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Medical Department of the US Army or the US Army Service at large.

1. Palareti G, Cosmi B, Legnani C, et al; for the PROLONG Investigators. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med*. 2006; 355(17):1780–1789. [LOE 1A]
2. Bruinstroop E, Klok FA, Van De Ree MA, Oosterwijk FL, Huisman MV. Elevated D-dimer levels predict recurrence in patients with idiopathic venous thromboembolism: a meta-analysis. *J Thromb Haemost*. 2009; 7(4):611–618. [LOE 1A]
3. Verhovsek M, Douketis JD, Yi Q, et al. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. *Ann Intern Med*. 2008; 149(7):481–490. [LOE 1A]
4. Zhu T, Martinez I, Emmerich J. Venous thromboembolism: risk factors for recurrence. *Arterioscler Thromb Vasc Biol*. 2009; 29(3):298–310. [LOE 1A]

Are NSAIDs safe for pain management in patients taking warfarin?

Evidence-Based Answer

Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of gastrointestinal (GI) bleeding in patients taking warfarin. (SOR: **B**, based on 1 cohort and 2 case-control studies.) The safety of cyclooxygenase-2 (COX-2) inhibitors is unproven in this clinical situation.

Two studies have looked at the patient-oriented outcome of GI hemorrhage. One retrospective cohort of 35,548 patients compared 3 groups: warfarin only (average age 67 years, average warfarin duration 373 days), warfarin plus a nonselective NSAID (average age 66.2 years, average warfarin duration 71 days), and warfarin plus a selective COX-2 inhibitor (average age 67.9 years, average warfarin duration 113 days).¹

Patients taking warfarin plus an NSAID were more likely to be hospitalized for GI bleeding than patients taking warfarin alone (adjusted hazard ratio [aHR] 3.6; 95% CI, 2.3–5.6). For patients taking warfarin plus a COX-2 inhibitor, the risk was not increased significantly above warfarin alone (aHR=1.7; 95% CI, 0.60–4.8).¹

Conversely, a 1-year nested case-control trial of 98,821 patients ≥66 years old who were continuously taking warfarin found case patients with admission for GI bleed (n=361) were more likely to be taking nonselective NSAIDs (OR 1.9; 95% CI, 1.4–3.7), celecoxib (OR 1.7; 95% CI, 1.2–3.6), or rofecoxib (OR 2.4; 95% CI, 1.7–3.6) in the preceding 90 days compared with controls (n=1,437).²

A case-control study from Korea evaluated 98 patients who were stable on warfarin when 1 of 8 NSAIDs was added. Thirty-nine patients (40%) had an increase in international normalized ratio (INR) ≥15% after starting the NSAIDs (cases). Controls were defined as the rest of the patients. The average age of cases and controls was 57.6 and 61.6 years, respectively.³

The authors performed a multivariate analysis and found 3 risk factors associated with INR elevation: high-dose warfarin >40 mg/wk (OR 19.46; 95% CI, 3.15–120.34); coadministration of interacting medications such as azole antifungals, statins, etc (OR 3.16; 95% CI, 1.17–8.54); and only 1 of the NSAIDs, meloxicam (OR 4.88; 95% CI, 1.23–19.45). During the

study, 5 patients had bleeding episodes: 1 intracranial hemorrhage, 2 epistaxis, 1 hemoptysis, and 1 muscle hematoma; none of them were taking meloxicam.³

Other studies using selective COX-2 inhibitors have focused on changes in the INR as the primary outcome. One RCT used a crossover design to compare the interaction of warfarin with rofecoxib 25 mg orally daily or celecoxib 200 mg orally daily, each administered for 3 weeks.⁴

Of the 16 men studied, 8 had an increase in INR ≥15% while on celecoxib and 8 had an increase while taking rofecoxib. Overall, no patient in the trial had an INR >4.0. Of the 4 patients with reported bleeding events (gingival bleeding and epistaxis), 3 had an INR outside the therapeutic range—2 taking celecoxib and 1 taking rofecoxib.⁴

A second RCT also used a crossover design to compare celecoxib (200 mg daily) and codeine (7–15 mg 3 or 4 times daily) when added to warfarin.⁵ This 10-week study found equal effect on the INR (mean difference 0.10; 95% CI –0.04 to 0.24; P=.16). Of the 15 patients in the trial, only 1 had an INR >4.5, which was during celecoxib use. EBP

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- Cheetham TG, Levy G, Niu F, Bixler F. Gastrointestinal safety of nonsteroidal antiinflammatory drugs and selective cyclooxygenase-2 inhibitors in patients on warfarin. *Ann Pharmacother.* 2009; 43(11):1765–1773. [LOE 2b]
- Battistella M, Mamdami MM, Juurlink DN, Rabeneck L, Laupacis A. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. *Arch Intern Med.* 2005; 165(2):189–192. [LOE 3b]
- Choi KH, Kim AJ, Son IJ, et al. Risk factors of drug interaction between warfarin and nonsteroidal anti-inflammatory drugs in practical setting. *J Korean Med Sci.* 2010; 25(3):337–341. [LOE 3b]
- Schaefer MG, Plowman BK, Morreale AP, Egan M. Interaction of rofecoxib and celecoxib with warfarin. *Am J Health Syst Pharm.* 2003; 60(13):1319–1323. [LOE 2b]
- Dentali F, Douketis JD, Woods K, et al. Does celecoxib potentiate the anticoagulant effect of warfarin? A randomized, double-blind, controlled trial. *Ann Pharmacother.* 2006; 40(7-8):1241–1247. [LOE 2b]

Evidence-Based Practice learning objectives

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

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eMedRef

Osteitis pubis

Inflammation of pubic symphysis and surrounding muscle insertions

- Common cause of groin pain in athletes
- Exact etiology unknown
 - May be due to repetitive microtrauma and/or shearing forces to pubic symphysis
 - Abnormal pelvic muscle biomechanics

Pathophysiology

- Pathology
 - Repetitive rotation of muscles inserting on pubic bone cause traction microtrauma to joint and surrounding fascia
- Prevalence
 - Seen in sports involving twisting, turning, kicking, lateral running, and running backwards
 - Soccer, ice hockey, football, track sprinting

Prevention

- Appropriate warm-up and stretching
 - Stress flexibility
- Proper biomechanics
 - Coach may need to be involved with technique
- Rest and recovery between workouts
- Core-strengthening exercises
- Appropriate footwear
 - Correct biomechanical issues
- Early recognition and treatment of symptoms
 - Avoid activities that cause pain

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Excessive daytime sleepiness

Excessive daytime sleepiness in a patient with insomnia suggests a comorbidity such as sleep-related breathing disorder or mood disorder

Diagnostics/ Treatment

- If primary problem, educate on lifestyle modifications, such as
 - Good sleep hygiene
 - Avoidance of stimulants
 - Avoidance of shift work
 - Limitation of naps to less than 45 minutes
- Consider modafinil as first-line agent as therapy for a patient with shift work disorder
- If secondary symptom, treat underlying cause
 - Diabetes control
 - Depression
 - Obesity
 - Neuropathic pain
 - Metabolic syndromes
 - Obstructive sleep apnea
 - Continuous positive airway pressure therapy leads to decline in daytime sleepiness and lower risk of motor vehicle accidents

Legal

Legal requirements for reporting excessive daytime sleepiness that may impair driving vary from state to state

- Treating physician has responsibility to make clinical assessment of patient's overall risk of unsafe driving with documentation of recommendations and precautions

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To review complete topic monograph visit
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In patients experiencing acute pain, how does the efficacy and gastrointestinal tolerability of tapentadol compare with oxycodone?

Bottom line

The analgesic effect of tapentadol (Nucynta®) immediate release (IR) 50 and 75 mg are comparable to oxycodone IR 10 mg, and tapentadol IR 100 mg to oxycodone IR 15 mg, for the treatment of acute pain. Tapentadol is associated with less nausea or vomiting than oxycodone at equianalgesic doses. (SOR: B, based on evidence from RCTs.)

Evidence summary

A recent RCT compared tapentadol IR, oxycodone IR, and placebo for postoperative pain relief after bunionectomy. A total of 603 patients were randomized to tapentadol IR 50 mg (n=119), 75 mg (n=120), or 100 mg (n=118); oxycodone IR 15 mg (n=125); or placebo (n=121) every 4 to 6 hours over a 72-hour period. The primary endpoint was the sum of the pain intensity difference (rated on an 11-point scale) over 48 hours (SPID48).¹

The mean SPID48 was significantly higher for all doses of tapentadol IR (50 mg, 119 points; 75 mg, 139 points; 100 mg, 167 points) and oxycodone IR 15 mg (172 points) compared with placebo (25 points; $P \leq .001$ for all comparisons).¹

Overall, the incidence of adverse effects was similar with all active treatments: tapentadol 50 mg, 70%; 75 mg, 75%; 100 mg, 85%; oxycodone 15 mg, 87% (vs placebo, 41%). A post hoc analysis showed significantly less nausea or vomiting in subjects using tapentadol IR 100 mg (53%) compared with the oxycodone IR 15 mg (70%; $P = .007$). The post hoc analysis also demonstrated that tapentadol IR 100 mg was noninferior to oxycodone IR 15 mg in analgesic effect.¹

Another RCT again compared the relative efficacy and tolerability of tapentadol IR and oxycodone IR in bunionectomy patients. A total of 901 patients were randomized to receive oral tapentadol IR 50 mg (n=275), 75 mg (n=278), oxycodone IR 10 mg (n=279), or placebo (n=69) every 4 to 6 hours for a 72-hour time period. The primary endpoint of this study was again the SPID48.²

The least squares mean difference from placebo SPID48 was statistically higher for both doses of tapentadol IR (50 mg, 62 points; 75 mg, 85 points) and oxycodone IR 10 mg (82 points) compared with placebo (all $P < .001$). A prespecified noninferiority analysis showed tapentadol IR 50 and 75 mg provided analgesia comparable to oxycodone IR 10 mg.²

Tapentadol IR 50 mg had a statistically significantly lower incidence of nausea or vomiting compared with oxycodone IR 10 mg (35% vs 59%, respectively; $P < .001$). In contrast, the incidence of nausea or vomiting with the 75-mg tapentadol IR dose was not different from oxycodone IR 10 mg (51% vs 59%, respectively; $P = .057$).²

Both studies were conducted by the same research groups. One of the groups is associated with the manufacturer of the product. EBP

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REFERENCES

1. Daniels SE, Upmalis D, Okamoto A, Lange C, Häussler J. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. *Curr Med Res Opin.* 2009; 25(3):765–776. [LOE 1b]
2. Daniels S, Casson E, Stegmann JU, et al. A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin.* 2009; 25(6):1551–1561. [LOE 1b]

GLOSSARY

ARR=absolute risk reduction	HR=hazard ratio	OR=odds ratio
CDC=Centers for Disease Control and Prevention	LOE=level of evidence	RCT=randomized controlled trial
CI=confidence interval	MRI=magnetic resonance imaging	RR=relative risk
CT=computed tomography	NNH=number needed to harm	SOR=strength of recommendation
FDA=US Food and Drug Administration	NNT=number needed to treat	

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1. Which of the following statements is true about the use of D-dimer testing in patients finishing vitamin K antagonist (VKA) therapy?

- a. The use of a D-dimer test 1 month after stopping VKA therapy can be used as a stand-alone test to determine a patient's risk for recurrence of another clot
- b. An elevated D-dimer value 1 month after stopping VKA therapy for a deep vein thrombosis (DVT) is a good indicator that the patient will not have another clotting event
- c. A normal D-dimer value 1 month after stopping VKA therapy for an unprovoked DVT is an indicator that the patient has a lower risk of venous thromboembolism (VTE) recurrence than if the D-dimer result were abnormal
- d. The use of D-dimer testing appears to have little value in helping the clinician determine which patients have the greatest potential for a recurrent VTE after initial treatment for an unprovoked VTE

2. After nail avulsion, the use of phenol to prevent nail regrowth:

- a. Is more effective than using sodium hydroxide
- b. Is more effective than surgical excision of the nail plate
- c. Reduces the rate of postoperative infections
- d. Decreases patient satisfaction because of early cosmetic problems

3. For men with diabetes and erectile dysfunction:

- a. Lifestyle modification significantly improves erectile function
- b. Tadalafil is significantly more effective than vardenafil
- c. Phosphodiesterase type 5 (PDE-5) inhibitors are significantly more effective than placebo
- d. Therapy must be individualized, as there are no clinical trials of erectile dysfunction in men with diabetes

4. What is the best way to delay or prevent the onset of type 2 diabetes in patients with glucose intolerance?

- a. Metformin
- b. Lifestyle modification
- c. Insulin
- d. Acarbose

5. When managing pain in a patient taking warfarin:

- a. Prescribing a nonsteroidal anti-inflammatory drug will increase the risk of hospitalization for a gastrointestinal bleed
- b. Prescribing a COX-2 inhibitor will decrease the risk of hospitalization below that of using warfarin alone
- c. Prescribing meloxicam is not associated with any changes in international normalized ratio (INR)
- d. The INR response to a COX-2 inhibitor is the same in all patients

6. Which statement is true about physical means for deep vein thrombosis (DVT) prophylaxis?

- a. There is a significant decrease in DVT after stroke in patients using graduated compression stockings compared with no compression
- b. There is a significant increase in DVT after stroke in patients using graduated compression stockings compared with no compression
- c. There is a significant increase in the occurrence of skin breakdown in patients wearing graduated compression stockings after stroke
- d. There is a significant decrease in the occurrence of skin breakdown in patients wearing graduated compression stockings after stroke

7. Which of the following doses of tapentadol immediate release (IR) is at least as effective as oxycodone IR 15 mg for acute pain?

- a. 50 mg
- b. 75 mg
- c. 100 mg
- d. All of the above doses

8. A patient is hospitalized with cellulitis, fever, diffuse sweating, and leukocytosis. The patient's blood and wound cultures are pending, but you suspect methicillin-resistant *Staphylococcus aureus* (MRSA) as the etiology. Which of the following statements is true regarding the best initial choice of antibiotic in hospitalized patients with MRSA cellulitis?

- a. Vancomycin is superior to linezolid
- b. Vancomycin is inferior to tigecycline
- c. Bactrim, clindamycin, or tetracycline are good choices
- d. Vancomycin is as effective as newer agents



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

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