Pearls from Tools for Practice

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Faculty/Presenter Disclosure

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JEOPARDY

Small Adults	Big Kids	Now	Grab Bag
Stopping vomiting in kids	A Flu Shot in the Dark	Treating Bell's Palsy	Are SSRI's safe in pregnancy
HPV Vaccine: The actual evidence	PSA screening for Cancer	Steroid shots for Tennis Elbow	Duoloxetine: Good for what ails yeh.
MSK Pain in kids	Overactive bladder & underactive meds	Back to the Spasm: Cyclobenzaprine & pain	Best Rheumatoid Test
AOM: Who to Treat	Colchicine gout: dose matters	NSAIDs & Fracture: Always & Never	E-cigarettes: solution or shifted harm.
Coughing up info on Croup	Cholinesterase meds and Dementia	Moves better than Serc: Vertigo	Sodium: the Spice of Life
Honey, I have cough	Who gets a BMD test	Do sore knees need steroids	FODMAP Diet
Treating Pediatric Fever	Old Iron Doses	Anti-virals for the flu: What evidence is there?	Melatonin: Sleepy time
Chasing away Infantile Hemangioma	Flashes of Evidence for Menopauses	Laceration: Time Matters (sort of)	Omega-3 & a world without CVD

What information is provided by TV Medical talk-shows

- Review of 40 episodes of 2 TV medical talk shows.
- Content of Recommendations: >90% benefit mentioned, ~40% benefit specific, 11-17% magnitude mentioned, 8-10% harms, costs 3-13%.
- Evidence for recommendations;
  - 46-63%: evidence found to agree
    - 33-53% overall: somewhat believable or believable.
  - 14-15%: evidence found to disagree*
  - 24%-39%: No evidence found*
- Bottom-Line: Patients need to be skeptical of recommendations offered on TV medical talk shows

BMJ. 2014 Dec 17;349:g7346..

What is the most efficient way to determine who is at high risk of osteoporosis and requires BMD?

- Evidence: 4 systematic reviews, up 72,000 women
  - OST as good or better than all others
  - Simple application of OST: **Weight (kg) - Age**
  - If ≥ 5, low risk (if <5, higher risk & BMD is warranted)
- New Study; 626 australians ≥70, OST vs FRAX

	FRAX (either Hip or Spine)	OST
Lumbar spine	12-19%	9%
Femoral Neck	8-10%	6%
Total Hip	6-9%	6%
Area Under Curve (Any Site)	0.64 – 0.76	0.76-0.82

#44 March 21, 2011 & J Am Geriatr Soc 62:442–446, 2014.

What is the most efficient way to determine who is at high risk of osteoporosis and requires BMD?

- **Bottom-line:** The OST is simple, quick and predicts osteoporosis as reliably as other more complicated instruments. It is a reasonable screening tool to identify those who would benefit from bone mineral density testing.
- Example: (Weight – Age) / 5 = if ≥1, then low risk.
  - Alternative: Weight – Age = if ≥5, then low risk
    - Weight in Kg, Age in years
  - 65 year old woman weighs 80kg
    - 80 – 65 = 15, low risk of osteoporosis.
  - A 60 year old woman weights 55kg
    - 55 – 60 = -5, risk of osteoporosis (BMD)

#44 March 21, 2011 & J Am Geriatr Soc 62:442–446, 2014.

In Macular Degeneration, do ocular vitamins decrease the progression?

- RCT (4757 pts): anti-oxidants (vitamin C 500mg; vitamin E 400IU; beta carotene 15mg) & zinc (80mg zinc) vs placebo.
  - Mean age 69 yrs, 56% females, x6.3 yrs
  - Baseline retinal photography: category 1 (minimal) - 4 (advanced)
    - 15 letter visual acuity loss: Category 2,3,4 patients: no diff
    - Category 3,4 pts: antioxidants + zinc (23%) vs placebo (29%), NNT 17
  - Progression to advanced AMD (predominantly neovascularization)
    - Category 3,4 patients: Statistically significant reduced progression with zinc NNT 17 and anti-oxidants + zinc NNT 13
- **Bottom-line:** Only in AMD patients with intermediate or greater retinal findings do ocular vitamins slow visual loss NNT 13. The risk of advanced AMD is rare in patients with minimal AMD, and ocular vitamins do not prevent AMD in those without AMD. Components of ocular vitamins are potentially harmful and should be used only in selective patients.

#85. March 18, 2013; CFP 2013 May; 59: 503.

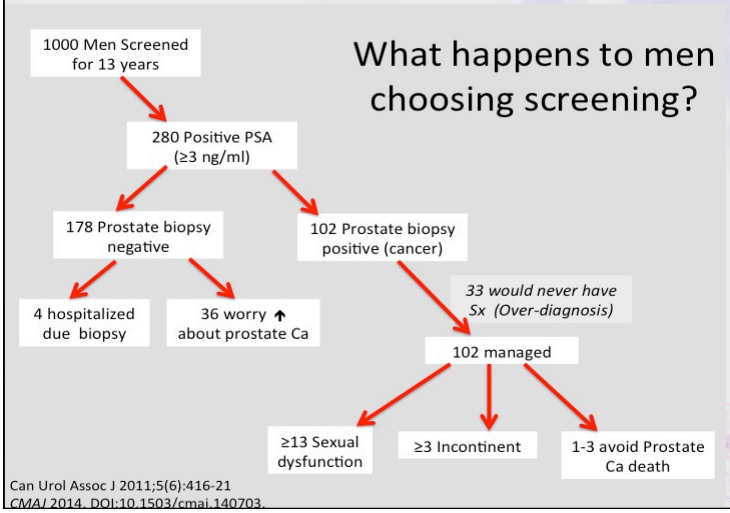
How much more sleep (if any) does melatonin give?

- Evidence: 6 sys revs, included 9-19 RCTs with 279-1683 pts
  - Falling asleep faster (4/6 meta-analyses ss): 4-11.7 minutes sooner.
    - "Sleep onset disorder" patients: 23 minutes sooner.
  - Increasing total sleep time: (4/6 meta-analyses ss): 8.2-18.2 minutes
  - Improving perceived sleep quality: SMD=0.22 (0.12-0.32).
  - Sleep efficiency (time asleep in bed, 2/4 meta-analyses ss): 1.9%-2.2%
  - Jet lag/shift workers: improved total sleep time, 18.2 minutes (8.1 to 29.3), but other outcomes not improved.
- **Bottom-line:** The quality of melatonin research is generally poor and at high risk of bias. If the results are believable, melatonin may help people fall asleep faster (~10 minutes) and spend more time asleep (~15 minutes).

TFP #120: September 2 2014.

What are the Risks and Benefits of PSA screening?

Time	NNS (Screen)	NNT
9 yrs	1410	48
14 yrs	293	12



- Bottom-Line: Men going for screening need a conversation about risks & benefit

Can Urol Assoc J 2011;5(6):416-21
CMAJ 2014. DOI:10.1503/cmaj.140703.

Will steroid injections improve or worsen tennis elbow (epicondylitis)?

- Evidence: 1 Sys Rev + 2 RCTs:
  - Sys Rev: 12 RCTs, 1171 patients
    - 3-7 wks: pain & function: steroid > no intervention or NSAIDs .
    - 26-52 wks: Steroid injections < no intervention.
  - RCT 198 patients: 3 wks steroid > physio or wait-&-see NNT 2
    - At 52 weeks: NNT=4 steroid worse outcomes than physio.
  - RCT 165: steroid vs steroid/physio vs physio vs placebo.
    - 4 wks: Steroid >physio NNT 4; 52 wks: physio/placebo > steroid NNT 10
- **Bottom-line:** Corticosteroid injections are effective for symptom management of lateral epicondylitis in the short-term, however in the long term they appear to result in poorer outcomes than no intervention at all.

TFP #48: July 27, 2011. JAMA 2013; 309(5): 461-9.

What is the appropriate dose in the elderly?

- RCT, 90 elderly anemic x2m (150, 50, 15mg)
  - Hgb ↑ significantly (14 Hgb points), no diff between doses
  - AE ↑ significantly as dose ↑, Dropout 15mg vs 150mg NNH=5
  - Abdominal cramps: NNH 2, Nausea/vomiting: NNH Constipation: NNH 5
- 15mg elemental iron = 2.5 ml's of Fer-In-Sol or ½ ferrous gluconate 300mg
- In pregnant & non-pregnant young women
  - Low dose reduced AE but not improve ferritin/Hgb as high dose
- Bottom-Line: Give low dose in elderly (AND check for cause) and full dose in young woman

TFP #30, November 2013 & Can Fam Physician 2015; 61: 159

Can Beta-blockers shrink infantile hemangiomas?

- Oral Propranolol: RCT (40 kids, age 9 wks-5 yrs, follow x 6 mon)
  - Vs placebo, propranolol 2mg/kg (divided 3x/day):
    - IH growth stopped by week 4 for all & Reduced volume at all weeks (example Wk 12: -48.5% vs. +17.9%).
  - Sys rev, (40 observational studies + RCT, 1,264 kids, age 6.6 mon):
    - Mean response (any improvement)=98% & Serious AE rare (<1%).
- Topical Timolol:
  - RCT (41 kids, 9 wks old). At 20-24 wks, one drop timolol maleate 0.5% gel BID vs placebo: Decreased in size by >5% (vs normal increase in size) NNT=3.
  - Prospective clinical study (124 kids, ≤12 months). At 4 months, IH stopped growing and/or became smaller, 92% vs 34%, NNT=2.
- **Bottom-line:** One small RCT and numerous observational studies demonstrate that oral propranolol stops growth and induces regression of infantile hemangiomas (IH) by four weeks. Similar evidence suggests topical timolol stops IH growth and induces regression by >5% after 4-6 months for every one in 2-3 patients.

TFP #123: October 14, 2014; Can Fam Physician. 2014;60(12):e590.

What is (are) required for Bell's Palsy Treatment

- Evidence: Meta-analysis, 2 high-quality RCTs
  - Unsatisfactory recovery at ≥4 months: corticosteroid 16% vs Placebo 26% (NNT 10)
  - Antivirals, with or without steroid, no additional benefit
- New meta-analysis: Anti-virals do not impact outcome - unless outcomes assessment is not blinded (ie detection bias).
- **Bottom-line:** The best evidence indicates that corticosteroids (in doses of prednisolone 25 mg BID or 60 mg x5 days then tapered by 10 mg/day) improve the odds of complete recovery from Bell's Palsy. Antivirals (used either alone or in addition to prednisolone) seem to offer no advantage (although research continues).

#4 July 9, 2009 Updated July 8, 2013. Turgeon RD Am J Med 2015

Can a single dose of Ondansetron improve outcomes in children with gastroenteritis?

- Evidence: Sys Rev 6 RCT + 1 RCT
  - Admission: ondansetron 7.5% vs placebo 14.6% (NNT 14)
  - Need for IV fluids: 13.9% vs 33.9% (NNT 5)
  - Still vomiting in emergency: 16.9% vs 37.8% (NNT 5)
  - Oral dose e.g.: 2mg=8-15kg, 4mg=15-30kg, 6-8mg= >30kg
- **Bottom-line**: While most cases of paediatric gastroenteritis are self-limiting, a single dose of oral ondansetron can help reduce vomiting, the need for IV fluids and likely admission.

#49 July 18, 2011.

Is Duloxetine Effective for Chronic Pain?

- Evidence: Meta-analysis (3 RCTs) & 5 RCTs vs other meds
- Versus Placebo: 3 RCTs with 1139 diabetic neuropathy pts
  - ≥50% improvement in pain: duloxetine 47% vs. placebo 29%, NNT=6
  - Adverse events d/c: duloxetine 13.9% vs placebo 8.3%, NNH=18
    - Nausea NNH 9, somnolence NNH 14, dry mouth NNH 17, dizziness NNH 21.
- Vs Others: all about equal. In one larger 804 neuropathy
  - Duloxetine 60mg vs Pregabalin 300mg: ≥50% improvement was 40% vs 28%, NNT 9 for Duloxetine (they were also the sponsors).
- **Bottom-line:** Compared to placebo, duloxetine appears efficacious in neuropathic pain, improving pain by 50% or more for one in six people. One in 18 people (over placebo) will have to quit due to adverse events.

TFP #103: Dec 16, 2013.

How much does HPV vaccine reduce CIN ≥2 lesions?

- Quadrivalent (HPV 6, 11, 16, 18) vaccine (Gardasil®):
  - FUTURE-1: 5,455 women x 4yrs. CIN≥2: 6.6% vs. 7.1%, not stat sign
    - External genital lesions (mostly condyloma): 3.8% vs. 5.7%, NNV=50.
  - FUTURE-2: 12,167 x3yrs. CIN≥2: 3.6% vs. 4.4% (placebo), NNV=125.
  - FUTURE 1/2 Combo: x 4yrs.
    - External genital lesions (mostly condyloma): 1.5% vs. 4%, NNV=40.
- Bivalent (HPV 16, 18 vaccine) (Cervarix®): 18,644 x4 yrs.
  - CIN≥2: 3.3% vs. 4.9% (placebo), NNV=60.
- Similar relative efficacy seen in males aged 16-26 (condyloma).
- **Bottom-line:** HPV vaccine is effective in preventing advanced cervical lesions (CIN≥2) in one in 60-125 women and condyloma in one in 40-50 men and women over 3-4 years.

TFP #125: Nov 10, 2014;.

In pediatric MSK injury, is ibuprofen or acetaminophen with codeine better?

- 336 children; ibuprofen, acetaminophen or codiene.
  - Ibuprofen >either (pain score & attaining "adequate" pain relief.
- 68 children; ibuprofen or aceta+codiene
  - No difference in pain scores.
- 336 children; ibuprofen vs acetaminophen+codeine
  - No difference pain scores, but Ibuprofen less functional limitation & AE
- 134 kids: oral morphine (0.5mg/kg) vs ibuprofen (10mg/kg)
  - No difference pain scores x4 dose (24 hrs), less AE 56% vs 31%

- **Bottom-line**: Ibuprofen provides better single-agent relief than acetaminophen or codeine, and is at least equivalent to acetaminophen with codeine or morphine for acute pediatric pain due to injury, with fewer adverse events.

TFP #14, updated July 8 2013 & CMAJ 2014. DOI:10.1503

Do Anti-cholinergics reduce trips to the bathroom ?

- Evidence: Sys rev, 61 RCTs, 11,956 pts, anticholinergic drugs
  - oxybutynin (Ditropan), tolterodine (Detrol), solifenacin (Vesicare) & darifenacin (Enablex)
  - Pt report cure/improve: 55.6% med vs 41% placebo, NNT=7
  - Meds reduced leaks 0.58/day vs placebo
  - Meds reduced micturitions 0.64/day vs placebo
  - Oxybutynin>Tolterodine: dry mouth (NNH 6), stop (NNH 20)
- **Bottom-line:** Both anticholinergic drugs and placebo improve overactive bladder, although medications slightly more (about ½ a trip less to the bathroom/day).

TFP #54: October 17, 2011.

Does Cyclobenzaprine improve improve Back Pain?

- Muscle relaxants vs placebo: 3 sys rev (9-46 RCTs, 820-5401 pts),
  - Pain: ~12 points on 100 VAS at 10 d
  - Pain target: NNT 4-7 at 2-7 days
- Cyclobenzaprine vs Placebo:
  - 1 Sys review (14 RCTs, 3023 pts): Global improve, NNT 3 at ~14 days
  - 2 RCTs on Dosing: 1384 patients at 7 days
    - Backache: 50% 5mg TID vs 38% placebo, NNT 9 (No diff: 5mg vs 10mg)
  - 2 RCTs of Extended or Immediate Release: 504 patients at 4 days
    - Global improve: NNT 7 (No diff: ER 30mg OD vs IR 10mg TID)
- Somnolence: 10% placebo, 29% for 5mg TID, 38% for 10mg TID
- **Bottom-line:** Cyclobenzaprine provides reduced pain and global improvement over placebo for one in every 3-9 patients in the first week. Cyclobenzaprine is as good or better than diazepam. Cyclobenzaprine 5mg TID is as effective as 10mg TID with less somnolence.

#143 July 20, 2015

Is Anti-CCP or Rheumatoid Factor better for RA?

- 7 sys revs of Anti-CCP in adult RA, 27-151 observational studies:
  - Sensitivity 53-71% & specificity 95-96%.
  - Likelihood Ratios: Positive LR 12.5-15.9 & negative LR 0.36-0.42.
- Higher-level (diagnostic cohort) & undifferentiated arthritis:
  - sensitivity generally lower (~54%) but specificity similar:
  - Positive Anti-CCP means RA likely but a negative does NOT rule out.
- **Bottom-line:** Anti-CCP, with ~96% specificity and ~14 positive likelihood ratio, is good for assisting with the diagnosis of RA. Anti-CCP is present in only ¼ to ½ of patients before or at diagnosis, so a negative test does NOT rule out RA. It can also predict more aggressive joint erosion.

TFP #146: Sept 14, 2015.

Are glucocorticoids beneficial for mild to moderate croup and is lower doses equivalent to standard doses?

- Evidence: Sys review (4299 patients) evaluating glucocoritcoids (mostly dexamethasone) mild-moderate croup found:
- Significant ↓ croup symptoms at 6 hrs: NNT = 5
- 2 small RCTs (137 patients): 0.15mg/kg vs 0.6mg/kg of Dexa found no difference in:
  - Change in croup score from baseline at 6 hours
  - Return visits and/or readmissions
- **Bottom-line**: Glucocorticoids are beneficial in treating mild to moderate croup, with a NNT of 5 for symptom improvement and a NNT of 17 for return to care. Low dose dexamethasone (0.15mg/kg) may be equivalent to the more commonly prescribed 0.6mg/kg

TFP #102: December 2, 2013

For patients with acute gout, is colchicine an effective treatment and when would its use be indicated?

- Evidence: Low dose (1.2 + 0.6 at 1 hr) vs Placebo,
  - 50% reduction in pain 38% vs 16% (NNT 5)
  - High dose no better but more side effects
  - Diarrhea: High dose NNH 2; Nausea NNH 8
- **Bottom-line:** Colchicine is a reasonable option for the treatment of acute gout, especially in patients in whom NSAIDs are contraindicated. Optimal dosing which balances treatment benefit with potential adverse events still remains to be determined, but low dose is recommended.

#57 November 29, 2011.

Does the influenza vaccine prevent influenza?

- Working age adults: Meta-analysis of 17 RCTS of 38,800:
  - Influenza rates: Well matched NNT=37 vs Poor match NNT=77
  - Hospitalization (2 trials) or pneumonia (1 trial), no diff
  - Most generalizable non-industry RCT American factory workers:
  - Influenza: Well-matched: vaccine 1.4%, placebo 10.2%, NNT=12.
    - Poor vaccine match: no difference.
- Age ≥65: highest-quality RCT, 1838 community dwelling seniors:
  - influenza: vaccine=1.7% vs placebo=4.2%, NNT=40
- **Bottom-line**: For healthy adults, the flu shot reduces the influenza rate with well-matched vaccine (NNT 12-37). Less in poorly matched vaccine. For community-dwelling seniors, the NNT is 40. Not shown to decrease hospitalizations and mortality benefit likely biased.

TFP #100 & 101: Can Fam Physician. 2014 Jan;60(1):50.

Does the Epley Maneuver fix one in 10 people?

- 6 sys revs: Epley maneuvers. Most recent (11 RCTs, 745 pts):
  - Epley vs control at 24 hrs-4 weeks, results statistically significant:
    - Resolution: 56% vs 21% with control, NNT=3.
    - Negative Dix-Hallpike: 80% vs 37% with control, NNT=3.
  - Small studies of Epley vs other maneuvers: other maneuvers equivalent (e.g. Semont and Gans Maneuvers) or inferior (e.g. Brandt-Droff)
- Post-Epley restrict movement (e.g. collar or sleep upright 1-2 days)
  - 2 sys revs: slight diff inclusion criteria (& conclusions):
    - Smaller one: no diff in resolution but ~11% more negative Dix-Hallpike.
- **Bottom-line:** Epley maneuvers will lead to the complete resolution of symptoms in every 2-3 patients treated. Post-Epley movement restriction does not improve symptom resolution but might promote a negative Dix-Hallpike for one in every 10 patients treated. (https://www.youtube.com/watch?v=9SLm76jQg3g)

#144 August 4, 2015

What is the optimal regimen for initiating insulin in type 2 diabetes?

- Evidence: 4 RCTs (primarily 1 of 708 pts x 3 yrs)
  - A1C similar but basal has less hypo & wgt gain
  - Family Doctors just as effective with A1c
  - Basal NPH, 10 units qhs, add 1 unit qhs, until fasting 4-7
- **Bottom-line**: In type 2 diabetes poorly controlled with oral agents, initiating basal insulin results in similar HbA1c reductions compared to prandial or biphasic insulin and may cause less weight gain and hypoglycemia. Family practitioners who start insulin are as effective as specialists.

#20 February 16, 2010. Updated Sept 16, 2013

Do omega-3 fatty acid supplements reduce the risk of recurrent CVD in patients with existing CVD?

- Evidence:
  - Meta-analysis (3 RCTS, 20485 CVD pts): No effect
  - RCT 12,536 diabetics (60% with CVD): No effect
  - RCT 12,153 CVD risk (30% with CVD): No effect
- **Bottom-line:** Although guidelines recommend increased dietary omega-3 consumption, evidence does not support using omega-3 fatty acid supplements to prevent recurrent CVD events in patients with cardiovascular disease.

#69 July 3, 2012. N Engl J Med. 2013;368:1800-8.

Do NSAIDs increase the risk of fractures not healing?

- Evidence: 3 RCTs
  - 2 adult (140 pts) colles #, flurbiprofen or piroxicam: No effect
  - 1 child (336 pts) arm #, ibuprofen: no effect.
  - One quasi-RCT: Less serious injuries or diff surgeries put in "non-NSAID" arm.
- Case control and cohort: Lots of confounding (e.g. differing injury)
  - Opioids also associated with non-union of fruacture
  - Non-Union overall is about 1-6%
- **Bottom-line**: Limited RCT data suggest that NSAIDs do not impair fracture healing. Cohort studies associating NSAID use with fracture non-union likely show non-healing (and painful) fractures are using more analgesics. As NSAIDs provide equivalent or superior acute pain relief, patients should not be denied their short-term use in fracture management. .

TFP #114.

Can E-cigs help even precontemplative people?

- 657 smokers: nicotine e-cigarettes (NEC), nicotine patches (NP), or placebo e-cigarettes (PEC) x12 wks. Motivated to quit & offered counseling. At 6 months:
  - Quitters: NEC 7.3%, NP 5.8%, PEC 4.1% (p =0.46)
  - ≥50% reduction: NEC 57% vs NP 41% (NNT 7) vs PEC 45% (no stat diff)
- 300 smokers: NEC, tapered dose nicotine (TNEC), or PEC, x12 wks. Not contemplating & not interested in cessation program. At 12 months (NEC & TNEC similar & combined):
  - Quitters: NEC 11.0%, PEC 4.0% (NNT = 15)
  - ≥50% reduction : NEC 14.5%, PEC 12.0% (no stat diff)
  - AE: RCTs no diff but Mouth / throat irritation most commonly reported
- **Bottom-line:** Compared to nicotine patches, smokers motivated to quit who used nicotine electronic cigarettes NECs had similar quit rates but a greater likelihood of decreasing daily cigarette consumption by ≥50% [Number needed to treat (NNT) of seven]. The long-term adverse effects and whether NECs lead to traditional cigarette use is unknown.

TFP October 2015. Elfrieda Cross & Michael R Kolber

Do OTC cough suppressants or Honey improve cough due to URTI in children?

- Evidence: 3 RCTs if Honey, all find the same
  - At 24 hrs: 59% honey, 45% DM & DPH, 31% no-drug
  - 8 RCTs of cough med (616 children): No effect
  - Health Canada recommends against OTC cough in <6
- **Bottom-line**: OTC cough suppressants should not be used in children under 6 and do not appear to be effective in older children. There is insufficient evidence to support the use of honey in acute pediatric cough.

#24 April 12, 2010. Updated October 22, 2013

Does screening asymptomatic patients in primary care for abdominal aortic aneurysm (AAA) alter mortality?

- Evidence: MASS RCT 67,800 men aged 65-74, U/S screening Prevalence of AAA (≥3 cm) = 4.9%.
  - At 10 yrs AAA mortality: 4.6/1000 screened, 8.7/1000 control
  - NNS = 238 x10 years to prevent 1 AAA-related death.
- Women: no effect.
- Annual risk of rupture by maximum diameter of aneursym:
  - < 4 cm = 0.5%, 4-4.9cm = 1%, 5-5.9 = 11%, 6-6.9cm = 26%
- **Bottom-line**: Ultrasound screening men for AAA (65-74 years) may confer a small AAA-related mortality benefit but does not change all-cause mortality. Population-based screening is not indicated for women.

TFP #75: October 15, 2012.

Is time the biggest concern in wound closure?

- Emergency dept cohort (three sites, 2,663 pts):
  - No sign diff in need for reassessment & infection (Abx Tx) at 30 days in closure <12 hrs (2.9%) vs >12 hrs (1.4%).
  - Limitations: Only 67% pt follow-up, low numbers in >12 hrs (n=72),
- Pediatrics cohort (2,834 children):
  - No diff in infection in closure <6 hrs (1.2%) vs >6 hrs (1.3%).
  - Limitations: No information on longer time periods.
- Neither cohort controlled for injury type or potential confounders
- Cross-sectional study (5,521) & 2 small studies confirm.
- **Bottom Line:** There is no evidence that a "golden period" exists in to repair simple, traumatic lacerations. Other patient and wound characteristics (e.g. diabetes, wound size, location, and contamination) are likely more predictive of infection. In the absence of evidence for maximum duration, clinical judgment/ experience and patient preferences should inform decisions.

TFP #141: June 22, 2015

How well do steroid shots work for knee OA?

- Evidence: 6 sys revs, (5-13 RCTs, 207-648 pts). often triamcinolone 20-40mg or methylprednisolone 40-120mg). Baseline pain 54 (out of 100)
  - Pain reduced: 21-22 points 1 wk, 16.5 points 2 wks, 7.4 points 3-4 wks
    - Average ~15 points better between 1-4 weeks, peak at 1.5 weeks
  - Global improve or pain reduction target: 74-78% steroid vs 45-54% placebo, NNT=3-5 at 1-4 weeks
  - After week 4, inconsistent results: most favorable was NNT 5 at 16-24 weeks (1 of 3 rev)
  - Function and stiffness: no consistent difference
- **Bottom-line:** Corticosteroid knee injections improve osteoarthritis pain ~40% more than placebo & one in every 3-5 patients will have global improvement x4 weeks. Long-term uncertain but serious adverse events are very rare (joint infection 1 in >14,000).

Unpublished TFP. Jamieson and Allan

When recommending regarding pediatric fever treatment, is acetaminophen or ibuprofen superior?

- Evidence: Meta-analysis of 10 trials,
  - Ibuprofen superior at 2, 4, and 6 hours; NNT 7
  - RCT: ibuprofen, acetaminophen, or both
  - combo ↓ fever in 24 hrs vs Aceta 4.4 hrs more, ibu 2.5
- Bottom-line: Treatment of paediatric fever is debated and should be discussed with parents/ patients. If clinicians are going to recommend a treatment, ibuprofen offers superior fever reduction with no increase in adverse events.

#28 June 7, 2010. Updated October 24 2013

Hot flash treatment with SSRI as good as HRT

- Evidence: Well-designed Meta-analysis of 43 RCT's
  - SSRI/SNRI (mid dose)= 1.13 ↓Hot Flashes/d (vs placebo)
  - Clonidine (≤0.075mg BID) = 0.95 - 1.63 ↓Hot flashes/d
  - Gabapentin (300mg TID) = 2.05 ↓Hot flashes/d
  - Soy Isoflavone Extract (50-70mg/d)= 0.97-1.22 ↓
  - Endometrial safety with Isoflavone still unresolved.
  - Estrogen best (2.5-3 ↓ Hot flashes/d)
- **Bottom-line:** All drugs for hot flashes are generally equivalent in effectiveness except HRT which is better. Select based on side-effects and patient preference.

JAMA 2006; 295: 2057-71..

What are the benefits and harms of cholinesterase inhibitors (ChEI) for Alzheimer's dementia

- Evidence: Over 20 meta-analyses, focus on Cochrane review of 13 trials (7,298 patients) and 4 other Sys reviews
  - ChEI vs. placebo statistically significant, but not clinically meaningful, mean change in cognition scores:
    - MMSE (out of 30): overall 1.37, varying from -0.04 to 1.37, depending on study
  - Number who had clinically meaningful improvement:
    - ADAS-Cog > 4 (out of 70): NNT = 6-18
  - Drop-out due to adverse events: NNH = 10 overall
- **Bottom-line:** Evidence for ChEI in Alzheimer's dementia is generally limited by small differences and high drop-out rates. Approximately one in ten patients show meaningful clinical improvement when treated for six months and ~1 in ten patients stop using the drug due to an adverse event.

TFP #107: February 18, 2014.

Is there an association between SSRI use in early pregnancy and cardiac birth defects (CBD)?

- 2 Sys REV, 9-13 studies, 20 444 -22412 exposures
  - CBD up, first trimester paroxetine: RR 1.43 (1.08-1.88), OR 1.44 (1.12-1.86)
  - Risk of CBD not statistically significant with other SSRIs:
    - Fluoxetine, Citalopram, Sertraline
- Cohort 46144 pregnant woman on any SSRI:
  - RR CBD: 1.29 (CI 1.13-1.38) but If restricted to depression only, no longer statistically significant: RR 1.06 (CI 0.96-1.22)
- **Bottom-line:** Observational studies demonstrate small increased risk of CBD with paroxetine use in early pregnancy with a number needed to harm of ~200. Evidence to support this association with other SSRIs is heterogeneous and less convincing.

Unpublished TFP. Dr Korownyk and Dr Mintzes

Amoxil will help 1 in 4 young kids with AOM?

- Evidence: 2 RCTs & a systematic review.
  - Avoid "treatment failure" day 8-12: NNT 3-9
  - Adverse events up: particularly diarrhea (NNH 5-7)
  - At 7-14 days, AOM will resolve in approximately 70% untreated children.
  - Poor Prognostic: Bilateral AOM, age <24 months, exposure to more children (day-care), and more severe symptom scores
- **Bottom-line**: Although most children will recover from AOM without complications, antibiotics will improve outcomes for 1 in 3 to 1 in 10, depending on outcome and complicating factors. They will cause adverse events, particularly diarrhea, in up to 1 in every 5.

TFP #90: May 27, 2013; CFP Volume 59: July 2013.

Is Na ≤3mg/d associated with lower CVD/mortality?

- Evidence: Systematic review of RCTs and large cohort studies
  - 7 RCTs with 6489 patients (3,900mg vs 3,000): hypertensive or normotensive for mortality or CVD: all no difference.
  - Reanalyzing with all pooled: CVD down RR=0.80 (0.64 to 0.99) but mortality no diff
- Cohort studies: 13 pooled (177,000 pts), higher salt ≈ higher stoke risk
  - Depends who is analyzing: 2 groups analyzed same cohort with different findings.
  - New data also raises: 102,000 from 17 countires. CVD or any cause death

Sodium level	**<3 gm**	**3-6 gm**	**6-7 gm**	**>7 gm**
Odds Ratio	1.27 (1.12-1.44)	1.0	1.05 (0.94-1.17)	1.15 (1.02-1.30)
Potassium Level	**<1.5 gm**	**1.5 – 3 gm**		**>3 gm**
Odds Ratio	1.0	0.81-0.86 (3 groups all significant)		0.78 (0.67-0.91)

- **Bottom-line:** Meta-analyses suggest that moderate sodium reduction (from 3900 mg to 3000 mg a day) can reduce CVD events, but the effect on mortality is unclear. More evidence with clinical outcomes is required to better define optimal levels of sodium intake.

TFP #82, Feb 13, 2013. N Engl J Med 2014;371:612-23.

Will FODMAPs resolve IBS in for 25% of patients?

- 4 RCTs, most young females, low FODMAP to normal diet :
  - Danish: 6-week, RCT, 123 patients, under specialist care
    - 500-pt scale (MCID=50): FODMAPs ~150 pts, probiotic ~80, ND ~30.
    - Sub-group analysis: Only diarrhea patients improved.
  - Australia: FODMAPS vs normal (3 wk cross-overs), 30 patients + 8 controls
    - Global GI Sx: 70% FODMAPs >10 pt improve (100-pt scale) but ND results not reported.
  - UK: 3 wk RCT 41 diarrhea or bloating IBS patients, under specialist care
    - "Adequate control": 68% FODMAPs, 23% Normal, NNT 3 (diff baseline)
  - Fourth RCT: Too short (two ds) to draw conclusions.
- **Bottom-line**: A low FODMAP diet may improve symptoms for patients with primarily diarrhea subtype irritable bowel syndrome (IBS). However, most studies were low quality (small numbers and short duration), and therefore more high quality studies are needed.

TFP #145: July 6, 2015.

Do neuramidase inhibitors (Tamiflu® or Relenza®) improve clinical outcomes in healthy patients with influenza?

- Evidence: 3 Sys Reviews: including >160,000 unpublished pages
  - Influenza Tx mostly healthy adults: oseltamivir (15 RCTs), zanamivir (14 RCTs)
    - Sx improvement reduced by 0.6 - 0.7 days (~10%)
    - Zanamivir ≈ "relief medications" (e.g. acetaminophen)
    - Pneumonia and hospitalization unchanged
  - Harm: Oseltamivir Nausea (NNH 28) vomiting (NNH 22)
  - Of 26 other systematic reviews, COI = 5x likely to report benefit & not report publication bias/low quality of studies
  - ≥1999, Oseltamivir >$18 billion, 1/2 =governments/company stockpiling
- **Bottom-line:** Highly biased, poor quality, mostly unpublished evidence demonstrates that oseltamivir (Tamiflu®) & zanamivir (Relenza®) shorten the duration of influenza symptoms by ~1/2 day. Objectively defined pneumonia or hospitalizations are not decreased.

Unpublished TFP: Korownyk and Kolber.

END