THE COLLEGE OF FAMILY PHYSICIANS OF CANADA

LE COLLÈGE DES MÉDECINS DE FAMILLE DU CANADA

Top 10 Self Learning Articles

Mike Allan, MD

Director

Programs and Practice Support

Samantha Moe, PharmD

Clinical Evidence Expert

Knowledge Experts and Tools Program

Conflict of Interest

Faculty: Mike Allan

Salary: College of Family Physicians of Canada, University of Alberta, Billing Income

Relationships with financial sponsors:

- Grants/Research Support: CIHR, PRIHS, Alberta Health, Alberta College of Family Physicians, Toward Optimized Practice, etc.
- Speaker's Bureau/Honoraria: Varying Provincial Chapters of CFP, University Departments of CPD, Others.
- Consulting Fees, Patents, Other: NA

Faculty: Samantha Moe

Salary: College of Family Physicians of Canada

Relationship with financial sponsors:

- Grants/research support: NA
- Speaker's Bureau/Honoraria: NA
- Consulting fees, Patents, Others: NA

Is cannabis use associated with an increased risk of schizophrenia?

Article: Review article.

Self Learning Quote: If cannabis used ≥50 times then 6x more likely to develop schizophrenia (over 15 years) than never users.

12 cohort studies: For 1 to 35 years & 591 to 50,053 patients. All positive odds ratio and 9 of 12 statistically significant.

Best (largest) study - (1.7 million patient years)

- Adjusted odds ratio was 1.8 (~doubling of baseline risk)
- Absolute risks of schizophrenia (unadjusted):
  - For never users = 0.7%
  - For ever users =1.5%
  - For users >50 times = 4.2% (yep: 4.2% is 6 times 0.7%)

World Psychiatry 2016;15:195–204)
Psychological Medicine (2012), 42, 1321–1328.

Is cannabis use associated with an increased risk of schizophrenia?

Other Articles:

- Systematic Review of cohorts: Any use - Adjusted OR 1.41 (1.20–1.65)
  - Regular Use OR = 2.09 (1.54–2.84).[1]
- Another Systematic Review: similar (Unadjusted OR 3.90 (2.84 - 5.34)) for higher users[2]
- If past psychosis: Continued cannabis use predicts higher relapse rates & longer hospital admissions.[3]

Caveats: observational & adjustment reduced effect[4] (but still significant)

Bottom-Line: Cannabis use is associated with an increased risk of schizophrenia. Over ~30 years, never users have a 0.7% chance, compared to 4.2% for regular users.

1) Lancet 2007; 370: 319–28.
2) Schizophrenia Bull 2016; 42(5): 1262–9.
3) Lancet Psychiatry 2016;3: 215–25.
4) Br J Psych 2008; 193, 357–63.

Is chronic use of PPIs associated with vitamin B12 deficiency, fracture, dementia, or C.difficile infections?

Article: Review article of PPI associated adverse events.

Self Learning Quote: 4 main areas reported. Chronic PPI associated with:

- B12 Deficiency: risk HR 1.83 (1.36-2.46). ? lowering pH, thus decreasing B12 absorption
- Fractures risk: NNH ~2,672 hip and 337 vertebral fractures, (using baseline risk without PPIs).
- New dementia: possible increased risk, adjusted HR 1.38 (1.04–1.83).
- C. difficile: increased incidence has a RR of 1.69 (1.40–1.97),
  - Highest risk = hospitalized on antibiotics, NNH 50 at 14 days
  - Recurrence of C. difficile also increased, HR 1.5 (1.1–2.0).
- 50% of chronic PPI use maybe unnecessary.

CMAJ. 2016;188(9):657-62

Is chronic use of PPIs associated with vitamin B12 deficiency, fracture, dementia, or C.difficile infections?

Other Articles:

- B12 Def: Newer systematic review adds little (similar studies)[1]
  - Absolute Risk (from cohort): Needing B12 treatment, 4.6% baseline but 11% on PPIs.[2]
- Fractures: Risk was ~16% baseline and ~22% for PPI users over ~6 years.[3]
  - Another study (of hip fracture) also found increase risk.[4]
- Dementia: 3 of 4 studies found PPI associated with higher risk (two were ~1.4).[5]
- C diff: 2 new meta-analysis, both finding very similar things.[6,7]
  - C diff incidence OR ~2.[6,7] Odds ratio ~1.7 for recurrence.[6]
  - Many studies during outbreaks: rates of 38% without PPI and 52% with.[6]
    - Estimation of risk after 14 days in hospital = 1.7% without versus 3.3% with PPI.[7]
  - All ages at risk[6,7] – peds, adults <65 and adults ≥65.

1) J Pharm Pract 2017; 30(6): 639-42.
2) J Clin Epi 2001; 54: 531–4.
3) J Bone Metab 2018;25(3):141-51
4) Rheumatology International 2018; 38:1999–2014.

5) J Gastroenterol Hepatol. 2017;32(8):1426-35.
6) J Gastroenterol 2018; 53:84–94.
7) World J Gastroenterol 2017; 23(35): 6500-15.

Is chronic use of PPIs associated with vitamin B12 deficiency, fracture, dementia, or C. difficile infections?

Caveats: All data is observational, at high risk of confounding.

Bottom-Line: There is relatively consistent evidence of potential increased of prolonged PPI use associated with B12 deficiency, fracture risk, dementia and C difficile infection. All the evidence is based on observational studies, leaving these associations at high risk of bias. Regardless though, these potential risks exists and the prolonged use of PPI in patients needs to be re-evaluated and PPI use stopped where feasible.

Does lowering or discontinuing PPIs cause an increase in GERD symptoms compared to continuing the PPI?

Article: Clinical Guideline

Self Learning Quote: Five studies - abrupt discontinuation and on demand PPI use vs continuous PPI use.

- Symptom relapse RR 1.71 (1.31-2.21), NNH 14
- Patient dissatisfaction with discontinuation RR 1.82 (1.26-2.56), NNH 14 vs continuous PPI use.
- Weekly pill burden reduced by ~4 pills

Other Articles:

- Open label RCT: Patients who completed 8-week course of PPI therapy.
  - Esomeprazole 40mg as needed vs esomeprazole 20mg OD for 12 weeks.[3]
- Results: patients symptoms and satisfaction not significantly different. Patients consumed less tablets/day on average.
- Limitation: Not double blinded and patients consumed same average mg of esomeprazole/day.

Can Fam Physician. 2017 May;63(5):354-364.
Cochrane Database Syst Rev. 2017 Mar 16;3:CD011969.

Does lowering or discontinuing PPIs cause an increase in GERD symptoms compared to continuing the PPI?

Bottom Line:

- CPG recommends PPIs be decreased/stopped/changed to prn in patients with resolution of GI symptoms following 4 weeks of PPI treatment.
- Relapse symptoms and dissatisfaction (NNH 14) may occur when switching to on-demand PPIs.
    - Implementation into practice may be difficult.
- Weekly pill burden could be reduced by about 4 pills.

Medicine (Baltimore). 2018 Oct;97(43):e12732.

Is ten days of bismuth quadruple therapy more effective than triple therapy for eradicating *H pylori*?

Article: Randomized, open label trial, 1620 patients with *H pylori* infection or positive ^{13}C-urea breath test

Self Learning Quote:

Bismuth based quadruple therapy	Non-bismuth based quadruple therapy	Triple therapy
Bismuth 300mg QID	Amoxicillin 1000mg BID	Amoxicillin 1000mg BID
Tetracycline 500 QID	Clarithromycin 500mg BID	Clarithromycin 500mg BID
Metronidazole 500mg TID	Metronidazole 500mg BID	--
All groups received lansoprazole 30mg BID		
10 days	10 days	14 days

- Age ~53 years
- 49% male
- 25% duodenal ulcer
- 39% gastric ulcer

Liou JM et al. The Lancet 2016; 388: 2355-65.

Is ten days of bismuth quadruple therapy more effective than triple therapy for eradicating *H pylori*?

	Bismuth-based quadruple therapy x 10 d	Non-bismuth based quadruple therapy x 10d	Triple therapy x 14d
Eradication rates	90%	86%	84%
Discontinuation due to side effects	10%	7%	4%
Poor adherence	9%	5%	3%

NNT 15

Dizziness, headache, nausea, vomiting, dark stool

Diarrhea
Taste Distortion

Is ten days of bismuth quadruple therapy more effective than triple therapy for eradicating *H pylori*?

Context/Other Research

Quadruple therapy is recommended as first line by guidelines[1]. This study and others[2,3]:

- Bismuth-based quadruple therapy (10-14 days) is more effective than 14 days of triple therapy
- Next best option is non-bismuth quadruple therapy x 14 days[3]

Bottom Line

Bismuth based quadruple therapy is 6% more effective than triple therapy at eradicating *H pylori* but is accompanied by slightly poorer tolerability and adherence rates. Bismuth quadruple therapy x 10 days may be an effective option, but non-bismuth based therapy should be prescribed for 14 days.

1. Fallone CA et al. Gastroenterology 2016; 151:51-69.
2. Uygun A et al. J Dig Dis 2007; 8: 211-15.
3. Songur Y et al. Am J Med Sci 2009; 338: 50-53.
4. Molina-Infante J. Alimen Pharmacol Therap 2015; 41(6): 581-9.

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Are blood pressure measurements over clothing equivalent to measurements on a bare arm?

Article: Controlled clinical trial in primary care of 186 patients.[1]

- Compared BP in different scenarios: bare arm vs sleeved arm

Self Learning Quote: 61% female, mean 75 y, 64% hypertensive

- Compared with bare arm, BP higher over sleeved arm (4/5mmHg, $p<0.001$)
- With greater age → more variability in BP
- Authors recommended against measuring BP over clothing

Other research: Controlled trial of 147 long term care residents[2]

- 76% women, mean age 87, 50% HTN
- Compared to bare arm, wearing shirt + sweater resulted in higher readings (8/9.5mmHg, $p<0.002$)

1. Ozone S et al. Family Practice 2016; 33 (5): 517-22.
2. Ozone et al. Blood Pressure Monitoring 2018; 23: 9-11.

Are blood pressure measurements over clothing equivalent to measurements on a bare arm?

Other Studies

Eight controlled trials[1-9] previously published:

- No meaningful differences in BP over bare vs sleeved arm (range: -1.7 to +1.0mmHg)
- Most used automated BP cuff, < 2mm clothing thickness

Caveats:

Differences between two newest trials and previous 8: may be differences in ages studied (newest trials: mean age 74-87; other studies: 44-62);

- Most studies included mix of patients with and without hypertension

Bottom Line: Perform blood pressure measurement over a bare arm whenever possible; measurements done over sleeved arm *in elderly patients* may result in higher and more variable readings

1. Holleman DR et al. J Gen Intern Med 1993; 8: 325-6.
2. Kahan E et al. Fam Prac 2003; 20(6):730-2
3. Ki JH et al. Korean J Fam Med 2013; 34: 145-51.
4. Liebl ME et al. Blood Pressure 2004; 13: 279-82.
5. Ma G et al. CMAJ 2008; 178(%): 585-9.
6. Pinar R et al. J Clin Nurs 2010; 19: 1861-4.
7. Thien T et al. Bl Press Monitor 2015; 20: 320-4.
8. Eder MJ et al. Dtsch Med Wochenschr 2008; 133: 1288-92.

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Does a negative urine culture mean there is no infection?

Article: An observational survey

Self Learning Quote:

- 220 women with Urinary Tract Symptoms (UTI) (dysuria, urinary urgency and/or frequency) versus 86 women without UTI symptoms.
- Bacterial urine culture compared to quantitative PCR.
- Women with UTI symptoms: 81% on urine culture and 96% on qPCR.
- Women without symptoms: 11% on urine culture and 12% on qPCR.
- Majority of cases (68% of samples) found E.Coli.

Clin Microbiol Infect. 2017 Sep;23(9):647-652.

Does a negative urine culture mean there is no infection?

Other Articles:

- RCT: If UTI symptoms but negative dipstick, 3-days of trimethoprim reduced symptoms.
- RCT: Minimal cost effectiveness differences between immediate antibiotics, delayed antibiotics (by 48 hours) and targeted Abx.

Limitations:

- Quantitative PCR is not used in practice
- Results only applicable to uncomplicated UTIs
- Majority of cases were E.coli, findings limited for non-E.Coli UTIs.

Bottom Line: A negative urine culture does not necessarily mean no infection. Symptoms are a stronger indicator and women can be treated immediately rather than wait for a culture.

BMJ. 2010 Feb 5;340:c346.
BMJ. 2005 Jul 16;331(7509):143.

Does targeting lower blood pressure in older adults have more benefits than harms?

Background: SPRINT is a RCT comparing intensive BP lowering (SBP<120mmHg) versus standard (SBP<140mmHg) among patients with high CV risk[1]

Article: A subgroup of elderly patients (>75 years old) studied in SPRINT trial, follow up 3y[2]

Self Learning Quote:

- N= 2636: mean age 80, 38% female, baseline BP 142/71, Framingham risk 25%, 30% frail
- Patients achieved mean SBP of 123mmHg vs 135mmHg, ~11mmHg difference
- Composite CV events: HR 0.66 (95% CI 0.51, 0.85), NNT 27
- All-cause mortality: HR 0.67 (0.49, 0.91) NNT 41
- Serious adverse events: no difference (48% vs 48%)
- Trend towards an increase in hypotension (HR 1.7, 0.97-3.09), syncope (HR 1.2, 0.76-2.00) and acute kidney injury (HR 1.4, 0.98, 2.04);
    - Patients with no underlying CKD: kidney injury risk greater with intense BP lowering (NNH 90)
    - Injurious falls and orthostatic hypotension: no different between groups

1. NEJM. 2015 Nov 26;373(22):2103-16.
2. JAMA. 2016 Jun 28;315(24):2673-82.

Does targeting lower BP in older adults have more benefits than harms?

Context/Other Studies

- General population: evidence supports BP<140/90, including diabetes and renal disease
- Results of SPRINT can be applied to patients >75 years but trial excludes many:
    - Diabetes, post-stroke, ejection fraction<35% or symptomatic HF, GFR < 20ml/min, BP<110 after 1min standing, diagnosis of dementia, nursing home residents

Bottom Line:

Over 3 years, an intense BP target lead to a reduction in CV events and all-cause mortality in older adults, compared to a standard target. If considered, ensure no exclusions; advise patient of potential harm. Check standing blood pressure prior to initiation and monitor electrolytes, creatinine and vitals.

Allan GM et al. TFP 2016, Article #37.
JAMA. 2016 Jun 28;315(24):2673-82.

Is there a correlation with Mini-Mental State Exam and driving risk in patients with dementia?

Article: Guidance document with review.

Self Learning Quote: Strongly consider driving risk if

- Family members concerned about driving safety.
- TMT-B (Trail Making Test-B): unsafe if ≥3 minutes to do or ≥3 errors (3 or 3 rule)
- TMT-A (Trail Making test-A): >48 seconds suggest need for driving evaluation.
- Other Features
  - Clock-drawing test predicts performance on a driving simulator.
  - Other tools/criteria: History of MVC or near crashes, MoCA ≤18, intersecting pentagrams.
  - CMA criteria: moderate dementia = trouble with 2 IADLs or 1 basic ADL
  - MMSE does not predict driving risk or motor vehicle crashes
- For TMT-B: Unclear safety if takes 2-3 minutes to do or 2 errors.
  - Likely safe if <2 minutes to do and <2 errors.

Is there a correlation with Mini-Mental State Exam and driving risk in patients with dementia?

Other articles:

- While not perfect,[1] TMT (A & B) can help assessment,[2,3] with TMT-B likely most helpful.[2]
- MOCA (cut-point ≤18) and clock drawing helpful as well.[3]
- Other studies point to the importance of family members concerns & past MVC or near MVC.[4]

Caveat: No RCT evidence.[5] No tests reliable by themselves

Bottom-Line: Several factors (family concerns, past/near MVC, MoCA, clock-drawing, and Trail Making Tests (A & B)) can help discerning drivers at risk (not MSE). None are definitive and referral for performance-based, comprehensive on-road driving evaluation provides the best assessment.

1) Age and Ageing 2013; 42: 577–581.
2) Int Psychogeriatr. 2009; 21(4):637-53.
3) Clin Geriatr Med 2018; 34:107–115.
4) J Am Geriatr Soc 2010; 58:1104–1108.
5) Cochrane Database Syst Rev. 2013; (5):CD006222.

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Are patients more likely to get reduced migraine frequency with melatonin or amitriptyline?

Article: Double-blind RCT (n= 178) with one year history migraine (± aura)

Self Learning Quote: Melatonin 3mg vs. amitriptyline 25mg vs. placebo x 12 weeks; 75% women, mean age 37

- Melatonin & amitriptyline had fewer migraine days/month (2.7, 2.2 days) than PLB (1.1days), $p<0.05$;
- Both better than placebo: ↓headache intensity (1.3 pt on 10-point scale), analgesic use (↓ 1/month), mean attack duration (↓ 4-5h)
- More responders (>50% improvement in headache frequency) with melatonin (54% vs 39% amitriptyline, abs diff 15%, NNT 6 over 12 weeks);

Goncalves AL et al. J Neurol Neurosurg Psychiatry 2016; 87: 1127-32.

Are patients more likely to get reduced migraine frequency with melatonin or amitriptyline?

Other Research

- Melatonin Systematic review (7 studies, mixed designs)[1]: placebo-controlled and comparator trials - conflicting results;
- RCT in pediatrics[2]: amitriptyline superior to melatonin for several outcomes including monthly frequency, severity, duration, # analgesics used

Bottom Line

Effectiveness of melatonin versus placebo or amitriptyline is inconsistent. While reasonable to try melatonin for migraine prevention, amitriptyline has consistently shown to be better than placebo with NNT 8 for headache severity and frequency.[3]

1. Long R et al. Medicine 2019; 98: 3.
2. Fallah R et al. Iran J Child Neurl 2018: 12(1): 47-54.
3. Allan et al. TFP 2015; #51.

Which complementary health products are effective for the common cold?

Article: Review article[1]

Self Learning Quote: 4 main areas reported.

- Probiotics: decrease occurrence of URTI (RR 0.62 (0.46-0.76)), perhaps shortened illness duration by ~2d (adults) but low quality evidence[2] ; well tolerated
  - *Other studies:* have shown similar results[3,4]
- Zinc lozenges or syrup: shortens illness by ~1d, but does not change severity[5]
  - SE: taste disturbance, nausea; loss of smell with nasal formulation (long-lasting)
  - *Other recent meta-analyses:* within 24h of onset of cold, zinc ≥ 75mg daily decreases duration of illness[6,7]; no effect on severity of colds;[6]
- Inconsistencies seen across studies for both probiotics and zinc

1. US Department of Health and Human Services, NIH. Flu and Colds. www.nccih.nih.gov
2. Hao Q et al. Cochrane Database Syst Rev. 2015 (2): CD006895.pub3.
3. Amaral MA et al. Pediatr Pulmonol 2017; 52; 833-43.
4. Wang Y et al. Medicine 2016; 95:31.
5. Singh M et al. Cochrane Review 2013; Issue 6. Art. No.: CD001364.
6. Science M et al. CMAJ 2012; DOI: 10.1503/cmaj.111990.
7. Hemila H et al. BMC Fam Practice 2015; 16: 24.

Which complementary health products are effective for the common cold?

Honey: small studies in children suggest superiority over placebo for reducing cough[1]

- *2018 updated review*[2] – after 3 days of therapy, honey associated with faster onset of relief (~3/4 day) compared with placebo and,
  - On 7-point scale: ↓ frequency (1 point) and severity (0.8 points), improves child & parent's sleep (1 point)
- Up to 3 days of treatment sufficient
- SE: gastrointestinal symptoms (12% vs 11% placebo, NNH 100)
- Data based on small number of trials, with small sample sizes

Saline: May have symptomatic benefit for common cold;

- Most recent meta-analysis[3]: n=5, small trials; most suggest no difference compared to placebo
- One larger trial: reduction in nasal secretion score, nasal breathing score[4] of ~ 0.3 on 4-point scales, small improvement and minimal clinical significance
  - Considerations: nasal discomfort and/or irritation; avoid tap water

1. Oduwole O et al. Cochrane Review 2014; Issue 12, Art. No.: CD 007094.
2. Oduwole O et al. Cochrane Review 2018; Issue 4, Art. No.: CD007094.
3. King D et al. Cochrane Database Syst Rev. 2015; (4): CD0006821.
4. Slapak et al. Arch Otolaryng 2008; 134(1): 67-74.

Which complementary health products treat and prevent the common cold?

Bottom Line:

For the treatment of common cold, probiotics and zinc may shorten the course of illness. Honey may have a small effect to relieve cough. Saline rinses may have a small to effect on nasal symptoms in some patients.

However, several limitations with data including few trials, small numbers of patients studied & inconsistent results across studies.

For the prevention of common cold, probiotics may decrease the incidence of common cold.

No evidence to support supplemental vitamin C, American ginseng, echinacea, and garlic for the treatment or prevention of the common cold.