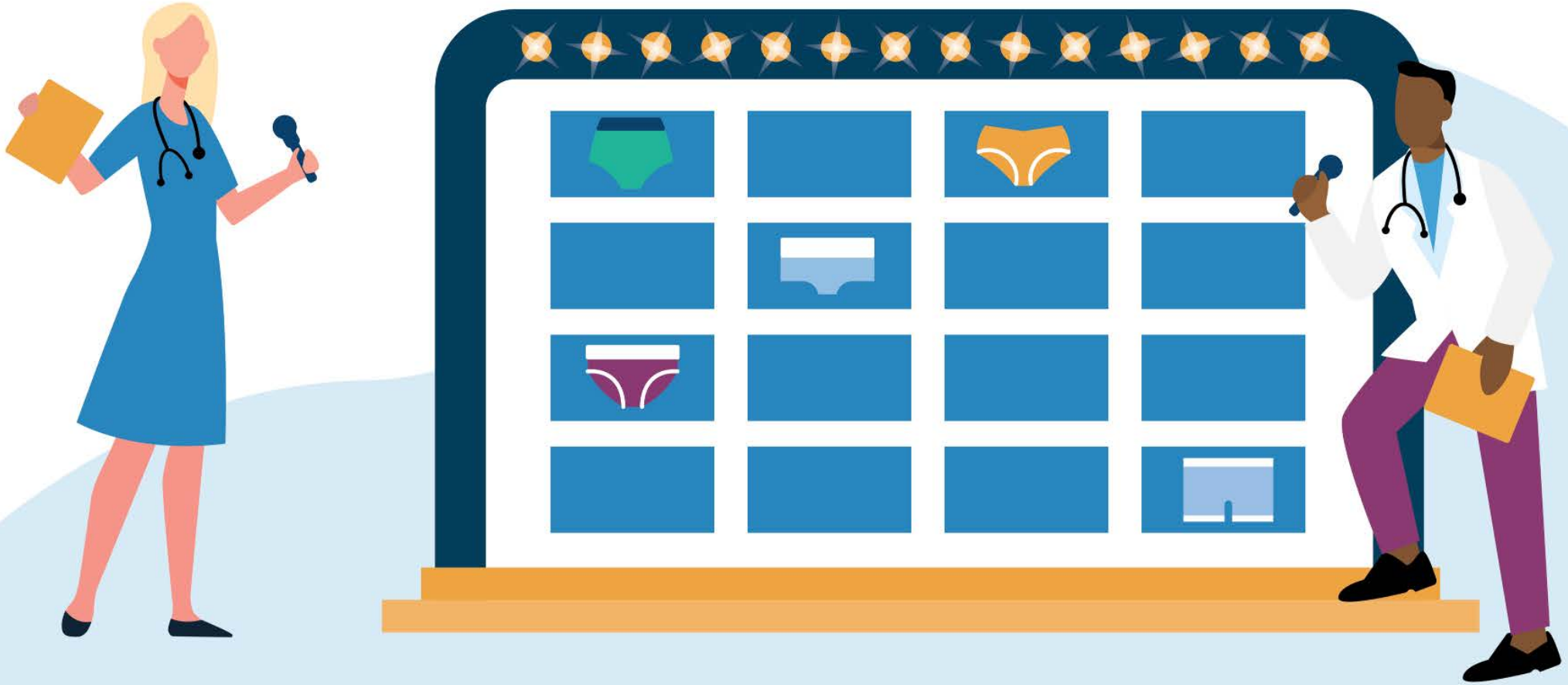

Choose Your Briefs

Covering the Essentials

Mike Kolber, Adrienne Lindblad and Samantha Moe

Presenter Disclosure: Mike Kolber

- Peace River family physician with special interest in GI
- Associate Director of PEER
- Relationships with Financial Sponsors: CIHR (BedMed Study)
- Any direct financial relationships including receipt of honoraria: ACFP, Alberta Health (Expert Drug Committee), SRPC, AMA, MEME, CFPC, Peterborough Health Team
- Membership on advisory boards or speakers' bureau: N/A
- Patents for drugs or devices: N/A
- Other: Employee of University of Alberta; EMP (Electronic Medical Procedure Reporting systems); Medical Director, Backcountry Ski Lodge

Presenter Disclosure: Adrienne Lindblad

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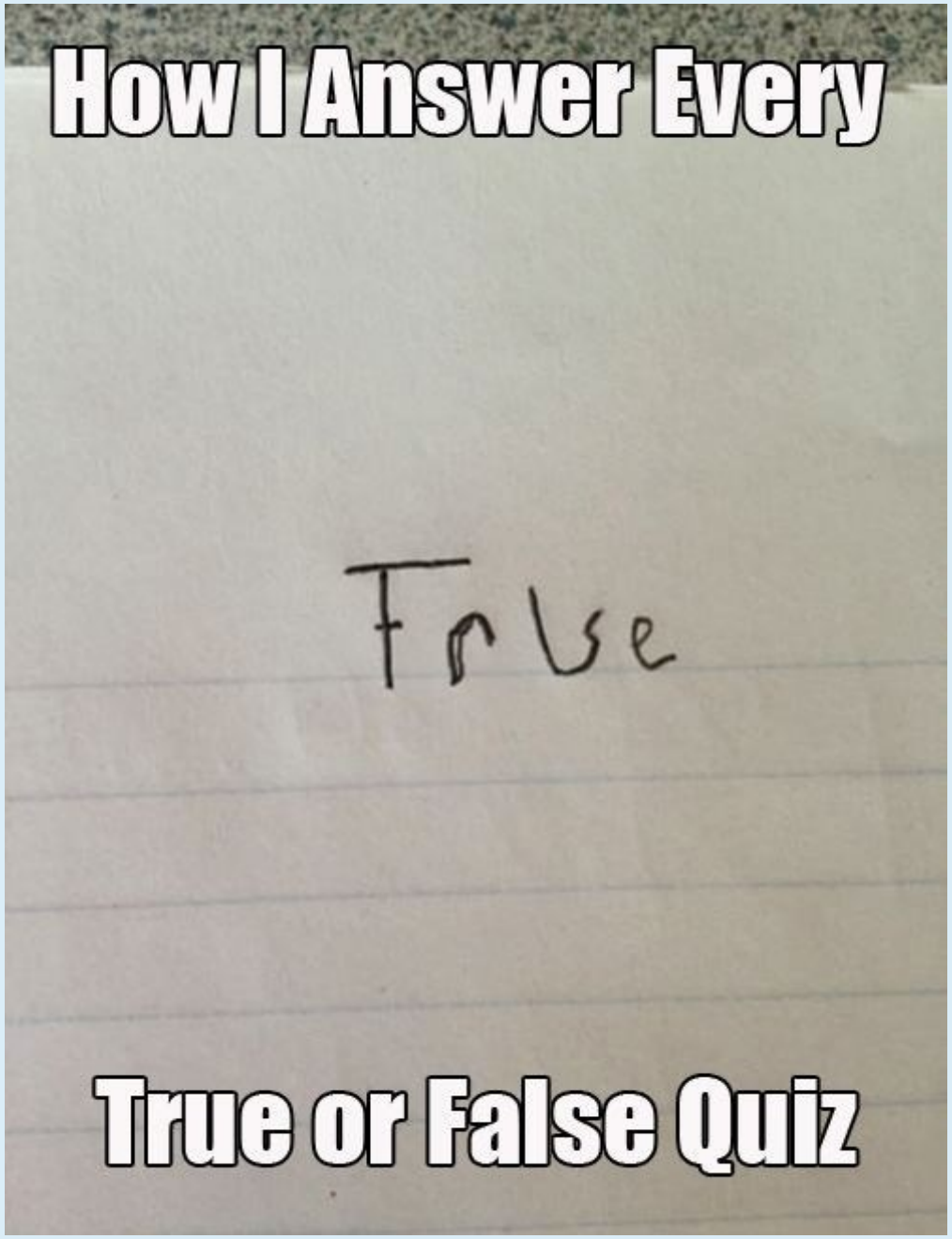
- Patents for drugs or devices: N/A
- Other: N/A

Presenter Disclosure: Samantha Moe

- Relationships with Financial Sponsors: Employee of the CFPC
- Any direct financial relationships including receipt of honoraria: N/A
- Membership on advisory boards or speakers' bureau: N/A
- Patents for drugs or devices: N/A
- Other: N/A

This isn’t a quiz …



	A	B	C	D
	Heart & Lung	Moms & babes	Weight loss … and more!	Catch All
1	Puffers for post-infectious cough	ASA in pregnancy	Orexin Inhibitors for insomnia	Uric Acid levels for gout
2	Icosapent for CV disease	Rest easy: infant sleep	Weight loss: Contrave	Treatment of high triglycerides
3	Forget about it? New drugs for dementia	TXA for heavy menstrual bleeding	Weight loss: Semaglutide	Compression stockings for cellulitis
4	Influenza vaccine for CAD prevention	PPIs for crying babies	New Years resolutions	ASA for post-joint arthroplasty
5	Chlorthalidone for hypertension	Fancy creams for scaly skin?	Antidepressants: Which one is best	A real fun guy: onychomycosis
6	Statins on cognition	A pain in the butt: anal fissures	DPP4 inhibitors for diabetes	Continuous glucose monitoring

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Do bronchodilators or inhaled steroids improve post-infectious cough in adults without asthma?

Inhaled steroids vs placebo: 4 SRs

- Most useful (2 RCTS, n=163), subacute cough (3-8 wks):
  - At 2 wks: placebo improved cough score ~50-56%, steroids improves 2-13% more
- Largest RCT (n=133): fluticasone 500mcg BID
  - Days off work, night awakenings, AE: no different
  - >50% cough improvement (non-smokers): 81% vs 54% placebo, NNT 4
  - No improvement among smokers
- Limitations: not all patients had post-infectious cough, industry funded

Bronchodilators vs placebo: one RCT (n=92)

- Salb/ipratrop nebulized vs placebo
- Ongoing cough (10d): 37% vs 69% placebo, NNT 3
- No diff at day 20
- Limitations: Small studies, non validated cough scores, multiple outcomes

Bottom line: data very limited. Post-infectious cough scores may improve ~50% on placebo and 5-10% more on ICS over 2 weeks. Bronchodilators may resolve cough in 63% at day 10 (31% on placebo) but most patients (regardless of treatment) have cough resolution by day 20.

TFP #329, December 2022

For infants with crying/irritability attributed to feeds, do PPIs improve symptoms over placebo without additional harms?

Two RCTS (PPIs):

- 162 infants (median 4mo): crying within 1h of ≥25% feeds; lansoprazole x 4 weeks
  - ≥50% reduction feedings w/ crying episodes/duration of episodes: 54% both
  - Crying, regurgitation, stopped feeds, feed refusal, back arching: no diff
  - Serious AE (e.g., RTI): 12% vs 2.5% placebo NNH 10
- 30 infants (mean 5mo) frequent crying and reflux confirmed on biopsy; omeprazole
  - Crying/fussiness, irritability: no difference
- H2RA vs PPI (one RCT): no difference
- Four withdrawal RCTs (8-268 infants, 1-11mo): open label treatment with PPI or famotidine x 1-4 weeks; responders randomized to continued drug or placebo (blinded):
  - At 4-5 weeks: vomiting, regurg, irritability, feeding difficulties, symptoms scores, AE – all no difference; weight – no difference

Bottom line: PPIs do not improve crying fussiness, irritability, regurgitation attributed to feeds. However, they may increase risk of serious AE (2.5% placebo vs 12%) at 4 weeks.

Do DPP-4 inhibitors improve patient-oriented outcomes?

- Four SRs, 3 RCTs (n=36,543) over ~2.5yrs vs placebo, DPP4-inhibitors:
  - Improved HbA1c: 0.3-0.5%
  - No effect on CVD outcomes (overall/CVD mortality, MI, or stroke) in those with or without previous CVD
  - Three other SRs (with smaller studies): found similar
- Microvascular: Neuropathy – no studies.
  - Retinopathy: MA (7 RCTs), DPP-4 increased risk (vs placebo):[11] NNH=430
  - Nephropathy: 2 MA & one large RCT (~7K pts)
    - Albuminuria: progression in 6% (DPP4) vs 7.5% placebo, NNH 67
    - Composite outcome (ESRD, death, or 40% decline GFR) vs placebo: no difference

Bottom-line: DPP-4 inhibitors have no effect on patient-oriented outcomes like CVD (ie. MI or stroke) or death. They increase the risk of hypoglycemia, pancreatitis and likely heart failure hospitalization. Second line therapies should focus on drugs that reduce patient- oriented outcomes.

Do statins negatively affect cognition, memory, or dementia?

Incidence of dementia

- 1 SR (one RCT, n=20,536), simv vs placebo. At five years, incidence was 0.3% in each group
- 3 newer RCTs (n=732-2361), statins vs placebo. At 5-7 years:
  - Largest RCT: no difference
  - Smaller RCTs: suggest statins reduce risk. (Ex:, 732 patients: cognitive impairment incidence: 11% vs 19% placebo, NNT 12)
- 6 SR obs studies, statins vs none (13-46 studies, mean 44-81y), followed 1-25y. Most reliable:
  - All-cause dementia (16 studies) RRR 15%
  - AD RRR 28%,
  - Vascular dementia: no diff

Cognition scores:

- 4 SR of RCTs, statins vs placebo in patients with or without cognitive impairmenet
- No difference: MMSE, ADL score, ADAS-cog, NPI
- Two RCTs found similar

Limitation: results of observational studies less reliable due to biases (e.g. 'healthy user effect' – lower risk patients more likely to use statins)

Bottom line: RCTs and large long term observational studies suggest no association between statins and risk of dementia or worsening cognition scores

Under Pressure: Compression stockings for recurrent cellulitis

RCT (n=84): edema for ≥3 months + history of cellulitis (≥2 episodes in 2y). Compression + education vs education. Compression individualized (primarily knee-high, 23-32 mmHg).

Outcomes @ 6 months

- Cellulitis recurrence: 15% compression vs 40% education, NNT=4.
- QOL: Improved 8 points (scale 0-100, higher better), NSS (study underpowered)
- Adherence: 88% wore garments ≥4 days/week. No AEs reported

Cohort (n=107 w/ chronic edema): compression, exercise, skin care provided in the community reduced incidence of cellulitis from 42 per 100py at baseline to 0 at 6-12 months

Context: ↑ compression (20-60mmHg) may be better for ↓ edema, but lower levels (10-20mmHg) also ↓edema and may ↑compliance. Price and coverage vary significantly. Price ↑ with strength

Contraindications: severe heart failure (risk of fluid overload) and critical limb ischemia.

Bottom Line: In patients with chronic leg edema and recurrent cellulitis, compression therapy decreases cellulitis recurrence (NNT=4) at 6 months. Compression stockings are a good treatment option for patients without contraindications, although real-world patient uptake may be limited.

What are risks & benefits of topical calcineurin inhibitors for atopic dermatitis?

Protopic (tacro); Elidel (pimecrolimus); tacrolimus 0.1% superior to 0.03% with similar SE.

Four MA	RCTs /patients	Improvement eczema symptoms		Notes
		CNI	Vehicle/steroid potency	
Tacrolimus 0.1%	2 RCTs; n=460	48-67%	16-38% (vehicle/low)	NNT 3-4 at 3wks
	2 RCTs; n=1540	73-93%	52-88% (mod-high)	4 RCTS (n=513): no diff at 2-44 wks
Pimecrolimus 1%	8 RCTs; n=2298	44%	22% (vehicle)	NNT 5 at 6wks
	1 RCT; n=2418	53%	51% (mild-moderate)	No difference
	2 RCTs, n=745	37-53%	**69-88%** (mod-high)	NNT 3-4 at 3wks favoring steroids
"Good response" (3 RCTs, n=543)		Tacrolimus 35%	Pimecrolimus 19%	NNT 7 at 2-6wks Network MA: no difference

- Adv effects: skin burning 30% vs 9% (steroid), (NNH 4);
- Cost (30g): Tacro 0.1% ~$103 vs betamethasone 0.1% ~$13.

Bottom Line: For improvement of AD, tacrolimus 0.1% is at least equivalent to moderate potency topical steroids. Pimecrolimus is better than placebo but likely inferior to moderate potency steroid and tacro 0.1%. Burning skin more common early (30-50% users; but tapers for most).

TFP #345, July 2023.

In adults with depression, which antidepressants are the best?

2011 systematic review (234 trials):

- No difference efficacy. Few stat differences not clinically important.
  - E.g., escitalopram 1.13 pts > citalopram on 60-point MADRS scale (MCID ≥2).
  - Similar # of pts had adverse events (61% had ≥1)
    - E.g. Venlafaxine 11% more N/V, sertraline 3% more diarrhea.

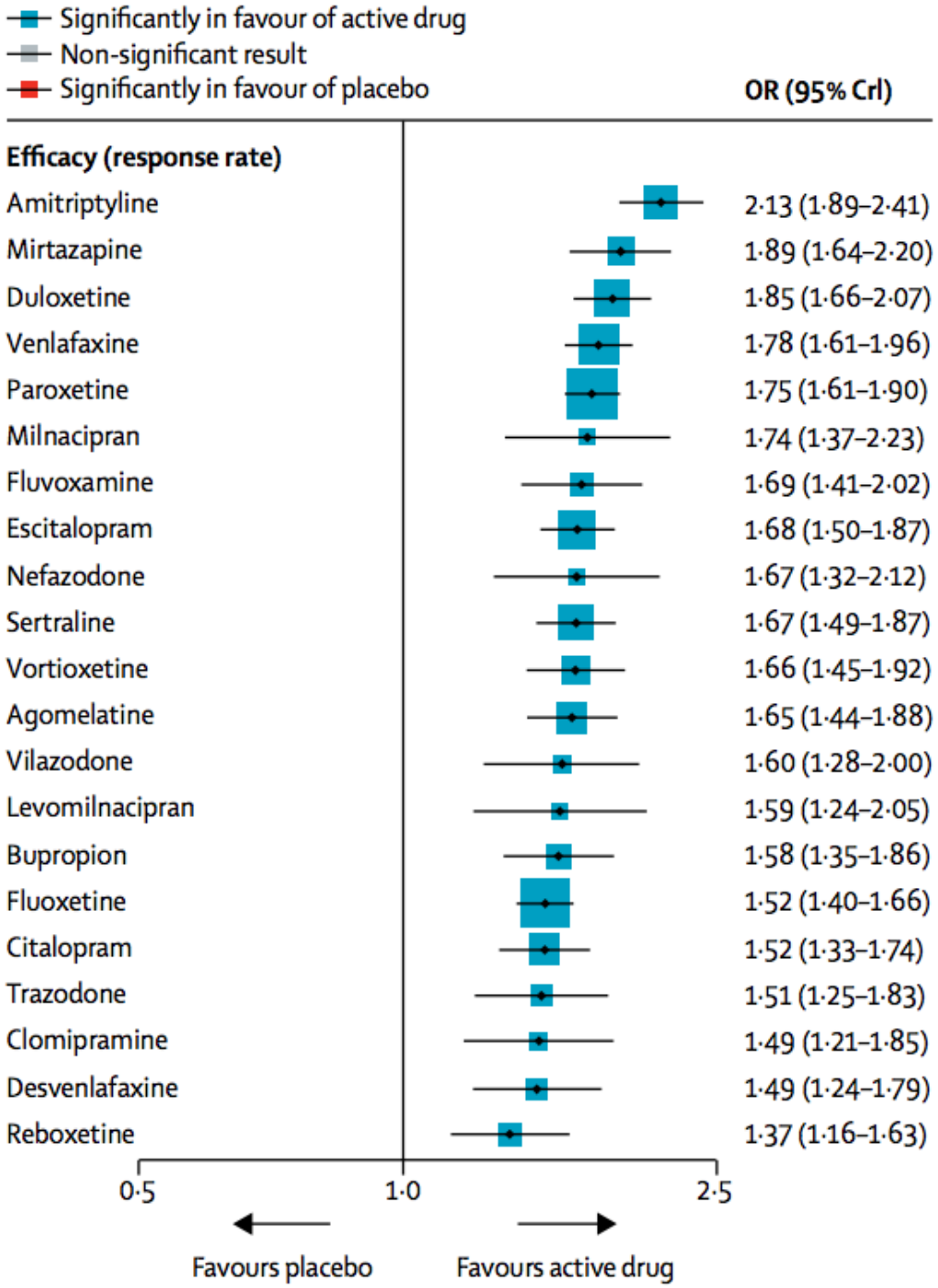
2009 systematic review (117 trials):

- Small differences efficacy & acceptability.
  - Efficacy: Mirtazapine, escitalopram, venlafaxine, sertraline.
  - Acceptability: Escitalopram, sertraline, bupropion, citalopram.

2018 systematic review (522 trials, 116,477 pts):

- All better than placebo, overlapping confidence intervals
- Did not report specific A/Es, most trials ~ 8 weeks duration

TFP #7, updated July 2016. Ciprani et al. Lancet 2018; 391:1357-66.



<u>Bottom Line:</u> there is little or no reliable difference in the efficacy or frequency of adverse events, but the types of adverse events may vary. Clinicians should select antidepressants based on adverse effects profile and cost, not on efficacy differences.

E.g. 90 days supply:

- Venlafaxine: $30
- Desvenlafaxine: $255

Does continuous glucose monitoring improve outcomes for adults with diabetes?

Real-time: automatically displays readings (e.g., Dexcom G6™) **Flash**: manual upload required (e.g., Freestyle Libre™).

- Evidence: SRs from last five years.
- Note: MCID HbA1c Δ: 0.5%.

Type 2 DMs (most on insulin):

- Real-time vs SMBG: 3 SRs (5 RCTs, 227-439 pts)
  - Severe hypoglycemia: none reported.
  - A1c: ↓ 0.25-0.5% with real-time over ~3-6 months.
- Flash vs SMBG**:** 1 SR (2 RCTs, 101-224 pts). At ~3-6 months:
  - Severe hypoglycemia, A1c: No difference.
  - D/C rates: 6% vs 15% (SMBG) (PEER calculation), NNT=12.

Type 1 DMs: ++ more patients: Real-time ↓ severe hypos ~2% (8 to 6%). Flash = no diff

Limitations: small #s, most RCTs unblinded, industry funded, inconsistent outcomes reported (satisfaction)

Bottom Line:

- **Severe hypos reduced in type 1 diabetics on real-time monitors (from ~8 to ~6%) compared to SMBG. Not in type 2s.**
- **Flash monitors don't change severe hypos in either DMs.**
- **Neither monitor provide consistently meaningful improvement in A1C in Type 1/Type 2s. Cost may limit use.**

TXA for HMB: will it slow the flow?

- 1 SR, 13 RCTs. Most data from individual RCTs
- Vs placebo (4 RCTs, 16-304 patients):
  - Improvement: 39% vs 11% placebo, NNT=4
  - Mean blood loss improvement: 40% vs 8% placebo
  - Sanitary items per cycle: ~5-10 fewer
  - AE: no difference
- Vs progestins (6 RCTs, 46-128 patients):
  - Improvement: 71% vs 46% progestins
  - Blood loss, sanitary item use: no difference
  - Flooding "better" 83% vs 45% progestin
  - AE: 21% vs 32% progestin (headaches, spotting)
- Vs levonorgestrel IUD (1 RCT, 42 patients):
  - Improvement: 29% vs 61% IUD
  - QOL, AE: no difference
- Vs mefenamic acid (1 RCT, 49 patients)
  - Improvement: 87% vs 61% MFA
  - Blood loss reduced from 164 to 75 ml versus 186-148 ml MFA
  - Sanitary items, bleeding duration, adverse events: no difference
- Many limitations…

Bottom Line: TXA is more effective than placebo, progestins, or NSAIDs. Menstrual blood loss is reduced in ~40% of women with TXA compared to ~10% with placebo, with 5-10 fewer sanitary items used/cycle and similar adverse events. However, more women benefit from a levonorgestrel IUD than TXA (~60% versus 30%). Effects on bleeding duration and flooding are inconsistent.

Infant Sleep Training

- 2 large RCTs, n=235-328, age 7 months, with “infant sleep problems”

1) 6-week RCT: sleep training (compared to safety education) reduced:
    - Severe sleep problems 4% vs 14%, NNT=10
    - # with >2 awakenings/night: 31% vs 60%, NNT=4

2) Cluster RCT. Sleep intervention (training) compared to usual care @ 10 months:
    - ↓ Infant sleep problems: 56% vs 68%, NNT=9
    - ↓ Mom’s with depression: 28% vs 35% (NSS)

At 2 years: reduced depressive symptoms 15% vs 26%, NNT=9

At 5 years: no diff in any outcome: child behaviour, mom mental health…

- **Bottom Line: Sleep training improves infant sleep problems with about 1 in 4 to 1 in 10 benefitting over no sleep training, with no adverse effects reported after 5 years. May also improve maternal mood.**

Toenail Onychomycosis

- Oral: meta-analysis 43 RCTs (9700 patients), example 65% nail involvement. Tx for 12-16 weeks. Follow-up 4 months-2 years. Clinical cure:
  - Terbinafine (8 RCTs) : 48% versus 6% placebo, NNT=3.
  - “Azoles” (9 RCTs): 31% versus 1% placebo, NNT=4.
  - Terbinafine vs azoles (15 RCTs): 58% versus 46%, NNT=9.
- Topicals: ~40% nail involvement, tx for 36-48 weeks. Clinical and micrological cure:
  - Ciclopirox: 3 RCTs, 6-8% versus 1% placebo, NNT=15-23.
  - Efinaconazole: 3 RCTs, 16-22% versus 4-9% placebo, NNT~9.
- **Bottom Line: Up to 45-60% of patients on oral treatments (terbinafine best), 6-22% on topicals (efinaconazole best), and <10% on placebo will be “cured” after ~1 year. Topicals should be reserved for cases with minimal (<40%) nail involvement.**

How effective are topical treatments for chronic anal fissures?

- Evidence: 5 systematic reviews in last 10 years. Unclear adjunctive treatments, healing usually determined on exam or patient reported. Focusing on most recent:
  - CCB (ex. diltiazem 2%): 4 RCTs, n=372. Healing @ 6 weeks: 78% vs 42% placebo, NNT=3
  - NTG (ex. Nitroglycerin 0.2-0.4%): 17 RCTs, n=1073. Healing @8 weeks: 63% vs 38% placebo, NNT=4
    - Lower in other SRs (50% vs 35%)
  - CCB vs NTG: 11 RCTs, n=720. Healing @ 8 weeks: 79% vs 65% NTG. Headache: 7% vs 56%
  - Topical Vit E: 1 open-label RCT, n=160. Healing @8 weeks: 86% vs 66% NTG, NNT=5. Stopping for headache: 0 vs 18% NTG. Unknown Vit E dose.
  - Cost: CCB/NTG ~$60/30g. Vit E as low as $10/50g
- **Bottom-line:** ~60% heal with topical nitroglycerins versus 40% on placebo at 8 weeks. Topical calcium channel blockers are at least as good, but better tolerated (7% vs 56% headache). Based on 1 RCT, topical vitamin E is also effective (86% healed vs 66% on NTG at 8 weeks).

Resolving New Year's Resolutions

- How long do resolutions last? (2 studies, 41-1066 participants)
  - Mean duration: 42 days.
  - 33-55% kept at one year
  - Mean slip-ups after 2 years: 14 (1 study, 200 people)
- Which resolutions are best kept? (1 study, 41 participants)
  - % kept at 11 months: 77% "goodness" versus 30% diet/exercise
- Should I suggest resolutions for others to follow? (1 study, 61 university students)
  - More likely to stick to personal goals than imposed ones.
  - Harms of suggesting resolutions to others not investigated.
- How much do resolutions cost?
  - $252 per person per year in Canada
- **Bottom Line: The average New Year's resolution is kept for 42 days. Resolutions aimed at "goodness" might be more likely followed. Suggesting resolutions to others, especially spouses and particularly around their weight, is never a good idea. A resolution to have no resolution could save an average of $250, but you can't put a price on following your dreams.**

TFP #330. December 19, 2022

Naltrexone/Bupropion (Contrave®)

- Systematic Review (4 RCTs, N=3955, 82% female, 56 weeks, baseline weight ~100kg)[1]
- Naltrexone/Bupropion vs placebo (+ lifestyle changes). At 56 weeks:
  - Weight loss (2 trials reporting): ~6 kg vs ~1 kg in control (4.5 kg vs 2 kg in other)
  - ≥5% weight loss: Naltrexone/Bupropion ~40-50% vs placebo ~20% (NNT 4)
  - ≥10% weight loss: Naltrexone/Bupropion ~25% vs placebo 9% (NNT 5)
- Withdrawals due to Adverse Events[1]: 25% versus 13% (**NNH 8**)
  - Nausea: 31% vs 7% placebo, NNH=5
  - Constipation: 18% vs 7%, NNH=10
  - Headache: 12% vs 7%, NNH=20
- Cost: ~$300-350/month
- **Bottom Line: Over 28-56 weeks, at best, ~50% of patients taking naltrexone/bupropion achieved a ≥5% loss in body weight, compared to ~20% in control. Naltrexone/bupropion adverse events (examples nausea, constipation) lead to withdrawal in 25% of patients versus 13% on placebo.**

Rx for Orexin Inhibitors?

- Most recent SR; 13 RCTs, 7875 participants.[1] Compared to placebo:
  - Fall asleep ~10 minutes faster, Total sleep time: 19 minutes more
  - Minutes awake after falling asleep: 9 minutes less; No difference in # awakenings
- Response to therapy (1 RCT)[2]: 55% vs 42% placebo (NNT=8)
- AE withdrawals (3 RCTs): no difference from placebo
  - Somnolence: 8% vs 2%, NNH=16; Abnormal dreams: 1.8% vs 0.8%, NNH=100; Dry mouth, nightmares, fatigue (all ~3%, NNH~50)
- RCT 1006 participants (63 yrs) Lembo vs zolpidem x1 month (lembo funded):
  - Sleep onset: 37 mins zolpidem, 23-26 mins lembo (baseline ~45 minutes)
    - Subjective: lembo 6 minutes better than zolp
  - Proportion of time asleep: no difference
  - Awake after falling asleep: lembo ranged from no diff to 19 mins better than zolp
  - “mild” sleep paralysis 4 lembo
  - AE leading to withdrawal: 2.7% zolp, ~1% lembo (somnolence, UTI, URTI)
- **Bottom Line: Orexin antagonists help people fall asleep ~9 minutes faster and increase total sleep time by ~19 minutes versus placebo over 1-3 months. About 8% of people taking orexin antagonists will experience next-day somnolence compared to 2% placebo.**

Weight loss and GLP-1: Semaglutide "Steps" up

4 RCTs: Semaglutide (2.4mg SQ/wk): BMI 38, 74% female, age 46; 68 wks

Design	Patients	Weight Loss (kg)	Attain ≥10% Loss	Other	D/C for Adverse Events (Nausea, as example)
General	1961	-15kg vs -3kg	69% vs 12%	QoL (from 65): +15 vs +5	D/C: 4.5% v 0.8% Nausea: 44% v 17%
+ Intense lifestyle	611	-17kg vs -6kg	75% vs 27%		D/C: 3.4% v 0% Nausea: 58% v 22%
Withdrawal (after 20 wks)	803	After stop: -7kg vs +6kg	79% vs 20%	Wt loss at 20wks: ~11kg	D/C: 2.4% v 2.2%, Nausea: 14% vs 5%

Bottom-Line: Large weight loss by itself or with intense lifestyle but effect gone when stops. GI distress is common (but few quit).

STEP studies: NEJM 2021;384:989-1002. JAMA 2021;325(14):1403-1413. JAMA 2021;325(14):1414-1425.

Putting semaglutide into context…

Semaglutide 2.4mg vs 1mg SC weekly (diabetic dose)

- Mean weight loss 10% versus 7% after 68 weeks, similar AE rates

Liraglutide 3mg SC daily: 2 RCTs (n=4500), mean wt 106kg

- Lost >10%: 33% vs 11% placebo, NNT 5 over 56 weeks
- Weight loss: ~3-5% at 1 year
- Withdrawal due to AE: 10% vs 4% placebo, NNH 17

Semaglutide 2.4mg weekly versus liraglutide 3mg SC daily (*new!)

- ≥10% weight loss: 71% versus 26% (NNT 2)
- Average percentage weight loss: ~16% vs 6.5%

Bottom Line: both agents effective for weight loss; semaglutide has more weight reduction than liraglutide based on industry-funded trials; dose titration (q4w) required; cost could limit use

TFP #168 (Aug 2016) and 295 (July 2021). JAMA 2022; 327(2)138-50.

Does Influenza vaccination reduce CV events?

- Evidence: from 5 SRs (5-8 RCTs, 4,211-12,029 patients, follow-up 1.5-12 months).
- Largest, highest-quality, multi-country (mostly European) RCT compared one-time influenza vax to placebo in 2,532 pts ≤3 days after MI. At 1 year:
  - Death: 2.9% vs 4.9% placebo.
  - CVEs (death, myocardial infarction, stent thrombosis): 5.3% vs 7.2% placebo.
  - AEs: Local injection reactions: ~5% absolute increase.
- Primary Prevention: no diff in CVE (2 RCTs; 12 total events)
- CHF patients: RCT of 5129 pts: vaccination: @ 2 years, CVEs: 15% vs 18% placebo (NSS)

Bottom Line: For every 100 patients vaccinated for influenza within ~1 month after an acute coronary syndrome, there will be 2 fewer CVEs and 2 fewer deaths at one year. The impact of influenza vaccination in primary cardiovascular prevention and other cardiovascular conditions is less clear.

ASA Post Joint arthroplasty for VTE prophylaxis?

- 3 publicly funded, non-inferiority RCTs. Symptomatic VTEs reported.

1. ASA vs LMWH: 778 Canadian THA; Dalteparin x10 days → dalteparin or ASA x 28 more days. Followed x 3 months:
   - VTE: ASA 0.3%, dalt 1.3%; major + non-major bleeds: ASA 0.5%, dalt 1.3% (both NSS)
2. ASA vs DOAC: 3424 Canadian THA + TKA; rivaroxaban x 5 days → Riva or ASA x 9 (knee) or 30 (hip) more days. At 3 months: VTE ~0.4%; Bleeds: ~0.9%

3. ASA vs LMWH immediately after surgery:[3] 9711 Aussie TKA/THAs → ASA 100mg or enoxaparin 40mg x 14 (knee) or 35 (hip) days. Study stopped early for LMWH superiority.

Outcomes at 90 days: VTE: ASA 3.5%, enoxaparin 1.8%; (p=0.007). Bleeding, mortality similar

Bottom Line: After initial treatment with 5 days of DOAC or 10 days LMWH, switching to ASA results in similar VTE and bleeding. Using ASA immediately after surgery results in more VTEs than LMWH. Due to cost/ease, transition to ASA for the remainder of VTE prophylaxis.

Targeting Uric Acid Levels in Gout

- Cohort studies find ↑ uric acid → ↑ likelihood of gout
- Best RCT: 183 pts on allopurinol (~270mg) with >3 flares in the past year and ↑ serum urate (~430 µmol/L). RCT: ↑ allopurinol (target UA <360 µmol/L) or continue current allopurinol dose
  - Outcomes @ 1 year: ≥1 gout flare: 54% escalating, 59% control: NSS
    - Tophi resolution, functional status, pain: no difference
    - Achieved UA level <360 µmol/L: 62% vs 32% control
- 2020 ACR Guidelines: recommend treat to UA <360 µmol/L[2]
  - We wrote authors: missed above RCT, included 3 RCTs of nurse or pharmacy led management (vs usual care) and possibly mislead by surrogates.[3]
    - Nurse: no target UA mentioned. Pharm: no diff in flares or clinical outcomes reported
- NZ RCT: 104 erosive gout → intense (<200 µmol/L) vs standard (<300): no diff in outcomes[4]

Bottom Line: Best evidence finds increasing doses of allopurinol to achieve a specific serum urate target (ex. <360 µmol/L) does not reduce gout flares, pain, or function, compared to standard allopurinol dosing.

TFP #262 2022, [2]Arthritis & Rheum 2020; 72(6): 744. [3]Arthritis & Rheum 2021, 73(3):543 [4]Arthritis & Rheum 2022; 74 (6): 1059

EPA (Icosapent) for CVD

Icosapent: REDUCE- IT: open label RCT 8179 pts: Icosapent 2g BID vs placebo (added to statin).

- 70% with CVD, 64 years, 72% ♂. Outcomes @ 5 years:
  - MACE: 17 vs 22% placebo, NNT=21; All-cause mortality: no diff
  - Atrial fibrillation: 5.3 vs 3.9% placebo, NNH 71 [hospital for AF: 3% vs 2% (NNH = 100)]
  - Serious Bleeding: 2.7 vs 2.1%: (NNH=167)

EPA ethyl ester: JELIS: 18,645 Japanese. RCT to EPA 1.8 g/day + statin vs statin alone

- 80% primary prevention, 61 years, 21% ♂. Outcomes @ 5 years:
  - Major coronary events: 2.8 vs 3.5% statin alone (NNT=143); All-cause death: no diff
  - "Hemorrhage": cerebral, fundal, epistaxis, subcutaneous: 1.1% vs 0.6%: NNH = 200
    - note excluded previous bleeders and previous arrythmias (did not report AF)

  D/C due to AEs: 11.7 vs 7.2% placebo, NNH 23

Sys Review: risk of AF (1.5%) and bleeding (0.5%)

Bottom-line: Icosapent ↓ MACE in high-risk (mostly 2' prevention) patients (17% vs 22% placebo). AF and bleeding increased. Cost ~$3600/year (and harms) should limit use.

TFP #277, Nov 2020, Lipid guideline update 2023

Chlorthalidone vs HCTZ for BP

- 1 recent SR including 1 large open label primary care RCT where 13,523 patients (97% ♂, age 72, SBP 139 mmHg, 10% w CVD) on HCTZ (95% 25 mg) randomized to switch to chlorthalidone 12.5-25 mg or continue HCTZ.
- Outcomes @ 2.4years:
  - CVEs: no diff (~10% each)
  - Hypo K (< 3.1 mmol/L): 5% vs 3.6% HCTZ (NNH=72)Hospitalized for hypo K: 1.5% vs 1.1% HCTZ (NNH=250)
- Previous TFPs:
  - chlorthalidone might be better than HCTZ for ↓ BP and ↓ CVEs
  - Hypo K: ~4% with diuretics: chlorthalidone 12.5-25mg ↓ K by ~0.2-0.4 mmol/L [0.1-0.2 mmol/L more than same dose of HCTZ].
  - 8% chlorthalidone users on K supplements @ 5 years.

Bottom Line: Chlorthalidone and HCTZ reduce CVE risk similarly, but risk of hypo K hospitalization ↑ ~0.4% over 2.4 years with chlorthalidone.

- TFP 347 Sep 2023, NEJM 2022; 387(26):2401, TFP 163 May 2016

ASA in Pregnancy

7 SRs (17-77 RCTs; 26,952-46,568 pts) comparing ASA (usually 12-28 weeks to delivery) to placebo in♀at varying pre-eclampsia risks.

- Babies: perinatal death: 2.1-3.1% vs 2.7-3.5% (placebo); NNT ~200
  - Preterm birth: ~16% vs 18% (placebo), NNT ~=50.
- Moms: pre-eclampsia: 4.5-9.6% vs 5.8-11.8% (placebo), NNT=31-72.
  - PPH (>0.5-1L): ~4-15% vs 3-14% (placebo), NNH ~100

Limitations: inconsistent definitions of 'at risk'; infrequent reporting of maternal outcomes; some large RCTs not in all SRs.

Guidelines: generally recommend ASA to women with:

- Any high-risk factor: ex: prior preeclampsia, hypertx, renal/autoimmune diseases, DM
- ≥2 moderate-risk factors (nulliparity, age >35-40 years, previous adverse pregnancy outcome).

Bottom Line: In women at risk for preeclampsia, ASA (50-150mg) reduces risk of perinatal death by ~0.5%, and preterm birth by ~2% compared to placebo. The risk of preeclampsia ↓ by ~2%, while PPH is increased by ~1%.

- TFP #349, October 2023

Treatment of Triglyceridemia (for pancreatitis)

- Sys rev of CV RCTs of fibrates (40,162 patients, mean baseline TGs 1.6-2.1 mmol/L) and statins (153,414 pts, mean baseline TGs 1.3-2.1 mmol/L). Pancreatitis @ ~5 years:
  - Fibrates: 0.4% vs 0.3% placebo.
  - Statins: 0.2% vs 0.3% placebo.
- No RCT examined triglyceride-lowering medications in pts w TGs ≥5.6 mmol/L.
- Large RCT comparing pemafibrate to placebo in 10,497 NIDDM patients, TGs 2.0-5.5 mmol/L
  - After 3.4 years: pancreatitis: 0.5% in both groups.

- Cohort study 1.5 million pts, 5-year risk of acute pancreatitis by TG:
  - 4.5-10mmol/L: 0.8%
  - 10-20 mmol/L: 1.5%
  - >20 mmol/L: 3.5%
- Guidelines recommend fibrates to ↓ TG pancreatitis; differ in thresholds (5.6-11.2 mmol/L)

Bottom Line: No RCTs have assessed the effect of fibrates (or other TG-lowering medications) on pancreatitis in patients with TGs ≥ 5.6 mmol/L. In patients with TGs <5.6 mmol/L, fibrates have no effect on pancreatitis or increase the absolute risk by ~0.1% over 5 years. Statins ↓ risk by 0.1%.

- TFP # 342, July 2023

Mabs for ADs (Alzheimer's).. Hint it's not the amyloid

- **Aducanumab**: IV q 4 weeks. ~3500 pts mild AD/MCI. Many issues with evidence / FDA decision:
  - RCTs stopped for futility, re-analysis found benefit (in 1 dose in 1 study). Unblinding due to harms (~40% ARIA), CDR-SB benefit <MCID, cost…
- **Lecanemab**: IV q 2 weeks: 1795 pts mild AD/MCI (MMSE 26). At 1.5 years:
  - Efficacy: multiple outcomes w/o adjustments.
    - Small change in CDR-SB and ADAS Cog (both < MCID)
  - AEs: DC due to AEs: 7% vs 3% (NNH = 25), infusion reactions (NNH=6), ARIA-H (NNH=12), ARIA-E (NNH=10), headache (NNH=33)
- **Donanemab: IV q 4w.** 1736 pts (MMSE 22) x 76 wks. Improvement in iADRS <MCID
  - 4 editorials for 1 RCT! (review, harms, costs, lack of ethnic diversity)
- **Solanezumab** ['pre-clinical' AD (75% w Fam History)] 1170 pts (MMSE 29). At 4.5 years: no diff in PACC score

Bottom-Line: Biologics improve brain Amyloid/Tau. Clinical effects are similar to placebo or below meaningful thresholds. Harms (and costs) are high. No evidence they are better than cholinesterase inhibitors.

- NEJM 2023; 388; 1: 9-21.2. Lancet Psychiatry 2021; 8: 1013-16. 3. Nature reviews 2023; 19: 132-133. JAMA 2023; doi: 10.1001/jama.2023.13239. 2. NEJM 2023; DOI: 10.1056/NEJMoa2305032