Top Research Studies of 2019: What’s New, What’s True, What’s Poo

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Faculty/Presenter Disclosures

• Faculty: Mike Allan

• Salary: College of Family Physicians of Canada, University of Alberta, Locum

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  • Patents: N/A
  • Other: 2 RCTs (public funded)
1) Review new studies that significantly modify present disease management.

2) Discuss recent research that confirms and advances our management.

3) Identify studies that got considerable coverage but may be misleading.
Eggs: Bad for you, Good for you, and Keto Stable

• Observational/cohort 29,615 participants x 17.5 years. 45% male.
  - Looking egg consumption and cholesterol intake on CVD and mortality

• Results: Lots of statistical tests (>100)
  - Average person has 1 to 2.5 eggs/week. Each additional 3.5 eggs/wk =
    - Increase CVD HR 1.06 (AR 1.1%)
    - Mortality HR 1.08 (AR 1.9%)
    - Nothing if adjust for cholesterol intake.
  - Cholesterol consumption seems to impact outcomes but maybe not if account for meat consumption. And, does not agree with other research.

**Bottom-Line:** Eggs do not seem risky. Even if real, you need a lot (go from 2.5 to 6 eggs/wk every week for 17 yrs), gives 1-2% increased risk.

Wait: Does weight impact diabetes?

- RCT of 298 primary care patients: DM <6yrs, BMI 27-45, not on insulin.
  - Diet replacement (Counterweight-Plus) ~840 kcal/day for 3 months (+ 2 optional) then slow re-intro. Stopped all DM and Hypertension drugs (added with monitoring)
  - In 2 yr follow-up if Wgt gain ≥2 kg, offered 2-4 week rescue
  - Baseline Mean patient = 54 y.o., 59% male, BMI 35, A1c 7.6%

- Results:
  - 1 yr: lost ≥15kg=0 vs 24% (NNT 5), Diabetes remission 4% vs 46% (NNT 3), Qol: down 3 vs up 7 (out of 100).
    - Remission by wt lost <5kg (7%), 5-10kg (34%), 10-15 (57%), & >15 (86%)
    - 2yr: lost ≥15kg=2% vs 11% (NNT 11), Diabetes remission 3% vs 36% (NNT 4), Qol: up 2 vs up 8 (out of 100).

- Bottom-Line: Surprise, weight loss can truly treat DM.

# Diabetes: Studies of Real Outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Population (risk)</th>
<th>Time (yrs)</th>
<th>Surrogate</th>
<th>CVD</th>
<th>Death</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapigliflozin</td>
<td>17160 (high)</td>
<td>4.2</td>
<td>A1c 0.4%, BP 2.7/0.7</td>
<td>NS (~0.5%)</td>
<td>NS (~0.5%)</td>
<td>DKA 0.3% v 0.1% Gen Inf 0.9 v 0.1%</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>4401 (Renal-High)</td>
<td>2.6</td>
<td>A1c 0.3%, BP 3.3/1</td>
<td>9.9% vs 12.2%</td>
<td>9.9% vs 12.2%</td>
<td>Renal death, transplant, dialysis =3.5% v 4.8%</td>
</tr>
</tbody>
</table>

### 4744 HF pts [2/3 Class II, 1/3 Class III], mostly max therapy, 42% diabetic. At 1.5 yrs,
- HF hospitalization or CVD death: 16% v 21%. (NNT ~21)
- Death from any Cause: 12% v 14% (NNT 44)

Dapigliflozin: likely a better CHF drug than a DM drug.
Canagliflozin: A drug that is helpful in diabetics with renal impairment.
## Diabetes: Studies of Real Outcomes

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<th>Time (yrs)</th>
<th>Surrogate</th>
<th>CVD</th>
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<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide</td>
<td>9901 (Lower)</td>
<td>5.4</td>
<td>A1c 0.6%, BP 1.7/0.5</td>
<td>12% vs 13.4%</td>
<td>NS (~1% less)</td>
<td>Microalbumin, + 3% quit A/E</td>
</tr>
<tr>
<td>Semaglutide (oral)</td>
<td>3183</td>
<td>1.3</td>
<td>A1c 0.7%, Wgt 3.4 kg</td>
<td>1.4% vs 2.8%</td>
<td>NS (~1%)</td>
<td></td>
</tr>
</tbody>
</table>

Dulaglutide: Small effect x5 years but mostly Primary Prevention  
Oral Semaglutide: Larger effect in x1.5 years but mostly Secondary Prevention
What’s Topical in Actinic Keratosis Treatment?

• 624 Dutch (mean age 73, 89% male). Multiple (mean 15) AK on face/vertex.
  - Only 8% level III (thicker keratosis) lesions.
  - 4 treatments: 5% Fluorouracil (5FU) cream, 5% imiquimod cream, methyl aminolevulinate photodynamic therapy (MAL-PDT), 0.015% ingenol mebutate

<table>
<thead>
<tr>
<th></th>
<th>Fluorouracil</th>
<th>Imiquimod</th>
<th>MAL-PDT</th>
<th>Ingenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥75% AKs Resolved</td>
<td>75%</td>
<td>54%</td>
<td>38%</td>
<td>29%</td>
</tr>
<tr>
<td>NNT for 5FU</td>
<td>-</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Erythema, erosions, vesicles, scaling</td>
<td>Pain/burning (NNH~2-3)</td>
<td>Same as 1st two</td>
<td></td>
</tr>
</tbody>
</table>

• **Bottom-Line:** Fluorouracil is the best field treatment for AK.
  - TFP: smaller RCTs, 5% FU had best numbers

Vitamin D Dose: Bigger is always better

- RCT (303 Calgarians): 400IU or 4000IU or 10,000 IU/day oral x 3 years
  - 54% male, mean age 62, mean Vit D level 79 nmol/L, mean BMD T-score ~0

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>400 IU/day</th>
<th>4,000 IU/day</th>
<th>10,000 IU/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Vitamin D Level (nmol/L)</td>
<td>77</td>
<td>132</td>
<td>144 (200 at 18 mon)</td>
</tr>
<tr>
<td>Loss of Bone Mass Radius</td>
<td>-1.2 %</td>
<td>-2.4%</td>
<td>-3.5%</td>
</tr>
<tr>
<td>Loss of Bone Mass Tibia</td>
<td>-0.4%</td>
<td>-1.0%</td>
<td>-1.7%</td>
</tr>
</tbody>
</table>

- Others similar
  - QoL, falls, fractures, stability testing, etc – No diff (study small + pt low risk)

- *4 RCTs (dose 60K/month - 500K/yr) - worse falls in 3 / worse fractures in 2.

**Bottom-Line:** Another study showing harms (albeit surrogate) of high dose vitamin D. Until we prove clear benefit, we should not give high doses.
5 Steps to get the most out of your Vitamins

1) Take the vitamins to a friends’ house ~2 km from your house. If you want to take your vitamin, walk to their house, pop the pill, walk home.

2) If you believe in higher dose vitamins, choose a home 5 kms from your house, run there at a comfortable pace, take two pills, and run home.
   • Note: You can just take one and get the same effect
   • Note 2: You can also take none

3) Put vitamins on your dinner plate with fresh and well seasoned/flavored vegetables, fruit, grains and protein. If compelled to try a vitamin, pick it up, lick it. How does it compare?

4) When you ingest more than the small amount of vitamins required for health, you pee out the excess. To avoid possible strain on your kidneys, place your vitamins directly into the toilet and flush.

5) Finally, if you really want your vitamins to work, package them up and send them to countries where vitamin deficiency are a serious health concern. The effect generosity may be the only supplement you need.
The facts, while interesting, are irrelevant.

- Family Doctors: Add 10 Primary Care doc/100,000: live 52 days longer
  - 10 more specialists: live 19 days longer.
- Is this new?
- No - This is True

- Starfield found:
  - >primary care = reduced mortality, CVD, cancer, etc
  - > specialist = worse mortality, CVD, Cancer, etc

- Others (2003):
  - Add 1 primary care physician = reduce 3.5 deaths per 10,000.
  - Add 1 specialty physician = increase 1.5 additional deaths per 10,000.”

Newest THC/CBD RCT

• 20 fibromyalgia – single doses 2 wks apart, x 4 products (cross-over)
  1. 22% THC and <1%CBD: Received 100 mg with 22.4-mg THC + ≤1-mg CBD.
  2. 6.3% THC and 8% CBD: Received 200 mg with 13.4-mg THC + 17.8-mg CBD.
  3. 9% CBD and <1% THC. Received 200 mg with <1-mg THC + 18.4-mg CBD
  4. Placebo

• Results:
  • Who got a ≥30% response,...
  • 90% THC/CBD, 65% THC, 55% placebo, 40% CBD
  • Drug High correlated with pain response
  • THC had more “psychedelic” effects,
  • Paranoid/anxiety and some AE (e.g. nausea) less with CBD

Bottom-Line: The effects are often not much over placebo, associated with being high & may depend on THC. CBD does have some less negative effects.

Is Cannabis the Solution to Opioid Overdose

- Ecological Study (whole state-wide data pooled)
  - Expanding to 2017,
    - Now reverse
  - Looking at different laws (like recreational, low THC medical cannabis, etc).
    - Nothing certain or positive

How long does a hip replacement last?

• Meta-analyses: 150 case series (44 usable) & Finland/Australia registries
  • Case Series = 13,212 hip replacements & registry = 215,676
  • Age ~58-74, 55-59% female, 62%-89% due to OA.

• Outcomes:

<table>
<thead>
<tr>
<th></th>
<th>≥15 years</th>
<th>≥20 years</th>
<th>≥25 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Case Series</td>
<td>86%</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>Country Registries</td>
<td>89%</td>
<td>70%</td>
<td>58%</td>
</tr>
</tbody>
</table>

• **Bottom Line:** Almost 90% of hip replacements last ≥15 years and 58-78% last ≥25 years.

The First Real “Treat to Target” RCT

- RCT 2860 pts (France & South Korea), recent ischemic CVA, x3.5 yrs
  - Mean age 66, 68% male, Public & industry funded.
  - Target LDL <1.8 vs 2.3-2.8 mmol/L

- Results: 3.5 mmol/L to 1.7 vs 2.5 mmol/L
  - Intense statin 24% vs 9%, Moderate 76% vs 71%, Statin/Ezetimibe 41% vs 7%
  - CVD events: HR=0.78, 9% vs 11%, NNT=42 (subgroups no sign but similar)
  - In “Treat to New Target” 2005 (high vs low dose atorvastatin in stable CVD)
    - Outcome: 9% vs 11% with HR=0.78

- **Bottom-Line:** Some confusing bits (ezetimibe) but overall, the theory supported by first trial. Still secondary and no evidence better than high dose

November 18, 2019, at NEJM.org. DOI: 10.1056/NEJMoa1910355
Wonder if this patient might benefit from an SSRI?

- RCT 655 patients, Sertraline 100-150mg vs placebo, x 12 weeks
  - GP felt “uncertainty about the possible benefit of an antidepressant.”
  - Done in UK, 41% male, 41% 18-34 years, PHQ-9 = 12 (out of 27)

- Results: PHQ-9 final score was 7 vs 8 (not stat diff). Remission not diff
  - Beck was 12 vs 15 (from 24) stat different. Remission 51% vs 39% (NNT 9)
  - Patient “feel better” = 59% vs 42% (NNT 6),
  - GAD score better, QoL (mental health) better, No diff in AE.

- **Bottom-Line:** Likely. Small improvements are seen overall (as most were mild-moderate) but overall about 60% vs 40% will feel better.

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Fluoxetine (10 RCTs, 956 pts): mean weight loss ~2.7kg x2-52 weeks

Silly RESEARCH
Kissing Makes it all Better!

• 30 allergic rhinitis & 30 atopic dermatitis
  • Age 29, 53% female, Japanese, “do not kiss habitually”
  • “kissed with lover or spouse freely for 30 min alone in a room with closed doors while listening to soft music”
  • The Beauty and the Beast, When You Wish Upon a Star, My Heart Will Go On, Love is a Many-Splendored Thing, Moon River, Sunrise Sunset, Can You Feel the Love Tonight.
  • Skin Prick Test
• Outcomes: 20-30% reduction in neurotrophins
  • Wheals: 8mm before & 5.4 after kissing (no diff if hugging)
• Bottom-Line: Kissing treats atopy. Dose and potency still unresolved.

The End