Showdown at the Evidence-Based Corral

Alan Dow, MD, MSHA
Virginia Commonwealth University
Nothing to disclose.
A 67 year old patient presents with untreated diabetic neuropathy. You consider gabapentin treatment. How many patients would you need to treat with gabapentin to result in moderate benefit for a single patient (the number needed to treat)?

A. 1
B. 3
C. 6
D. 10
E. 20
<table>
<thead>
<tr>
<th>Disease state</th>
<th>Parameter</th>
<th>Number needed to treat or harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Neuropathy</td>
<td>&gt;50% benefit</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>&gt;25% benefit</td>
<td>6.6</td>
</tr>
<tr>
<td>Postherpetic Neuropathy</td>
<td>&gt;50% benefit</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>&gt;25% benefit</td>
<td>4.8</td>
</tr>
<tr>
<td>Harm</td>
<td>Adverse event</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Serious adverse event</td>
<td>∞</td>
</tr>
</tbody>
</table>

GABAPENTIN "Johnnies" ABUSE

And The Best Rehab Centers For Treatment

Gabapentin can cause side-effects, withdrawal symptoms, and overdose whether it's being abused, or used for its legitimate medical purpose.
Gabapentin for neuropathy

- Moderately efficacious
  - Number needed to treat about 6
- Minimal harm to individuals
- Larger societal risk

- Monitor benefit using a simple tool such as the PGIC
Question

A 68 yo female presents with new onset heart failure with preserved ejection fraction (HFpEF). Which of the following medication classes is most likely to increase her lifespan?

1. A beta-blocker
2. An ACE inhibitor
3. A mineralocorticoid receptor antagonist
4. An angiotension receptor blocker
5. Digoxin
## All Cause Mortality

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Studies</th>
<th>Risk ratio (lower is better)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>3 trials, 1046 subjects</td>
<td>0.78 (0.65-0.94)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>4 trials, 1234 subjects</td>
<td>1.10 (0.85-1.43)</td>
</tr>
<tr>
<td>ARBs</td>
<td>3 trials, 7257 subjects</td>
<td>1.02 (0.93-1.12)</td>
</tr>
<tr>
<td>Mineralcorticoid-receptor antagonists</td>
<td>2 trials, 3867 subjects</td>
<td>0.92 (0.79-1.08)</td>
</tr>
<tr>
<td>Others</td>
<td>1 trial each of amlodipine, doxazosin, digoxin, and sildenafil</td>
<td>No benefit (though amlodipine needs more study)</td>
</tr>
</tbody>
</table>

Zheng SL et al. Heart. 2017
HFpEF

- CV mortality
  - Similar results for mortality
- Hospitalizations
  - Benefit of mineralcorticoid receptor antagonists ($p = 0.05$, 3445 patients)
  - Lack of benefit for beta-blockers ($p = 0.10$, 382 patients)
- Beta-blockers (and diuretics) are my first-line therapy for HFpEF
A 69 year-old man with COPD has O2 saturations at rest of 90% and with exercise of 85%. He continues to smoke, and you are apprehensive about giving him oxygen. Which of the following would be the best course of action?

1. Oxygen with sleep only
2. Oxygen 24 hours a day
3. Oxygen intermittently based on his symptoms
4. No oxygen
738 pts with stable COPD and:
- resting O2 sats of 89-93% and/or
- exercise-induced O2 sats of 80-90%

Followed for six years:
- Death or first hospitalization
- COPD exacerbations
- Quality of life and functional measures

Long-term Supplemental Oxygen (368 pts)
No oxygen (370 pts)

A Primary Outcome (Death or First Hospitalization) or First Hospitalization

- Supplemental oxygen, primary outcome
- Supplemental oxygen, first hospitalization
- No supplemental oxygen, primary outcome
- No supplemental oxygen, first hospitalization

Cumulative Probability

Death or first hospitalization, P=0.52 by log-rank test
First hospitalization, P=0.37 by log-rank test

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>No supplemental oxygen</th>
<th>Supplemental oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>370 304 232 181 139 102 76 59 43 29 21 7 1</td>
<td>368 314 243 198 158 125 86 61 44 24 13 6 1</td>
</tr>
</tbody>
</table>

Death

Cumulative Probability

No supplemental oxygen
Supplemental oxygen

P=0.53 by log-rank test

No. at Risk
No supplemental oxygen: 370, 366, 362, 319, 295, 242, 210, 177, 152, 120, 88, 33, 10
Supplemental oxygen: 368, 366, 358, 321, 294, 245, 216, 184, 149, 116, 88, 33, 8

51 adverse events due to oxygen:
- 23 falls
- 2 hospitalizations
- 6 fires
Conclusions

Supplemental oxygen may not be beneficial for patients with moderate desaturations
  • And has risk
How will insurers react?
  • Medicare spent 2 billion on O2 for COPD pts in 2011
Question

You are caring for a 75 year old man with terminal lung cancer. He has been admitted for delirium. What is the next best step in management of his delirium?

1. Add haloperidol 0.5 BID and titrate to effect.
2. Add risperidone 0.5 BID and titrate to effect.
3. Add clonazepam 0.5 mg BID and titrate to effect.
4. Do not start any new medication for delirium management.
247 patients receiving inpatient palliative care and who have delirium

- 82 received haloperidol (0.5 mg BID titrated)
- 81 received risperidone (0.5 mg BID titrated)
- 84 received placebo (0.5 mg BID titrated)

2.5 mg of midazolam added for severe symptoms in all patients

Outcomes
- Delirium scores on day 3
- Survival
- Side effects
- Other scored measures

No. at risk
Placebo  84  63  59  55
Risperidone  82  58  49  39
Haloperidol  81  64  55  51
Median survival:
- Haloperidol – 16 days
- Risperidone – 17 days
- Placebo – 26 days
(significant difference)

Other findings

- Midazolam use lower with placebo ($p = 0.02$)
- More extrapyramidal side effects with both drugs ($p<0.05$)
Conclusions

- In palliative care patients, delirium is best managed without haloperidol and risperidone.
- Presumptive drug therapy for delirium does more harm than good.
A 74 yo female presented for fatigue. Evaluation has been unremarkable except for a TSH = 6.4 (ULN = 4.5) and a free T4 that is normal. What is your next step?

1. Start levothyroxine 50 mcg daily
2. Repeat TSH only in 6 weeks
3. Repeat TSH and free T4 in 6 weeks
4. Reassure and follow symptomatically
737 adults over 65 with TSH = 4.6 – 19.00 and normal free T4

25-50 micrograms of levothyroxine

Placebo

Outcomes
• Hypothyroid Symptoms score and Tiredness score at 1 year
• Functional and other measures

Stott DJ et al. NEJM. 2017.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention group change over year 1</th>
<th>P value vs control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroid symptom score</td>
<td>0.9</td>
<td>0.99</td>
</tr>
<tr>
<td>Tiredness score</td>
<td>2.8</td>
<td>0.77</td>
</tr>
<tr>
<td>Hand grip strength</td>
<td>0.5</td>
<td>0.84</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>-2.9 mmHg</td>
<td>0.90</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.2</td>
<td>0.89</td>
</tr>
<tr>
<td>Hyperthyroid symptom score</td>
<td>0.0</td>
<td>0.35</td>
</tr>
</tbody>
</table>

No difference between groups in aFib, fracture, CHF.

Stott DJ et al. NEJM. 2017.
Conclusions

Starting levothyroxine in the setting of a high TSH and normal free T4 provides no benefit

• Lack of benefit to TSH = 20
A 72 yo female presents with recurrent knee pain secondary to osteoarthritis. You are considering initiating steroid injections. How should you counsel her?

1. Steroid injections will help with the pain and not have long-term effects on the knee.
2. Steroid injections will help with the pain but have long-term, negative effects on the knee.
3. Steroid injections will not help with the pain and have long-term, negative effects on the knee.
4. Steroid injections will neither help with the pain nor have long-term, negative effects on the knee.
140 pts with knee osteoarthritis and moderate pain

- Triamcinolone injection every 3 months x 2 years (n=70)
- Saline injection every 3 months x 2 years (n=70)

Outcomes:
- Pain scores
- Knee cartilage volume by MRI
- Other outcomes
<table>
<thead>
<tr>
<th>2-year change</th>
<th>Intervention</th>
<th>Control</th>
<th>Significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage thickness</td>
<td>-0.29 mm</td>
<td>-0.13 mm</td>
<td>0.04</td>
</tr>
<tr>
<td>Cartilage damage index</td>
<td>-177.63</td>
<td>-82.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Pain scores</td>
<td>-1.2</td>
<td>-1.9</td>
<td>0.17</td>
</tr>
<tr>
<td>20-m walk</td>
<td>-0.29</td>
<td>0.14</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Other findings

• No change in tibial or hip bone density
• No change in hypertension outcomes
• A1Cs actually worse in saline group
• More adverse events in saline group (63 vs 52, p=0.02)
Conclusions

Two years of intraarticular steroids for knee osteoarthritis:
• Did not improve pain
• Led to harm in terms of cartilage loss

What about fewer injections?
Questions and discussion

Alan Dow, MD, MSHA
alan.dow@vcuhealth.org