Morphine, gabapentin, or their combination for neuropathic pain

Study Type: POEM
Purpose: Does the combination of morphine and gabapentin reduce pain and side effects when compared to either agent alone for diabetic neuropathy or postherpetic neuralgia.
Study Duration: 12 weeks, 4 weeks crossover
Trial Design: double-blind, placebo-controlled, randomized, crossover, single-center
Patients were crossed over every 5 weeks (doses were tapered during the 5th week with a 3 day washout)
Drug and target doses: All drugs and doses were titrated depending on the patient - morphine (120 mg) vs gabapentin (3200 mg) vs active placebo (1.6 mg lorazepam) vs combination (morphine 60 mg, 2400 mg gabapentin)
active placebo = low-dose lorazepam (no neuropathic pain effects of benzodiazepines)
Small patients and elderly patients had different target doses (~ half of the doses above)
Patients: 57 patients, 35 patients with diabetic neuropathy and 22 patients with postherpetic neuralgia, mean age 64, ~58% male, 74 kg, 98% white, ~5 years of pain duration, those with diabetic neuropathy had diabetes at least 10 years with HbA1c of 8, baseline pain intensity score = 5.7, concomitant meds - ~70% on nothing, 10% on TCA, 6% on SSRI, ~3% on anticonvulsants, 30% on NSAID’s
Inclusion: daily moderate pain for more than 3 months, age 18 to 89, normal liver function, SCr < 1.5, language skills
Exclusion: recent MI, unstable angina, CHF, central neurologic disorders including seizures, history of alcohol and drug abuse, pregnancy, lack of a primary care physician.
Outcomes:
Primary end point: Pain intensity scale (0 to 10) rated three times a day
Secondary measures: Adverse events; Short-Form McGill Pain Questionnaire (higher number, severe pain); Brief Pain Inventory (0 to 10, 10 = complete pain-related interference), Beck Depression Inventory (0 to 63, higher number, severe depression); General Health Survey (0 to 100, higher number, better quality of life); MMSE

1. Are the results valid?
* randomized? yes
* double-blinded? yes
* were groups similar? yes
* allocation concealment? yes
* all patients accounted for? yes

2. What were the results:

<table>
<thead>
<tr>
<th>Pain Intensity Score Baseline</th>
<th>Placebo</th>
<th>Gabapentin</th>
<th>Morphine</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.7</td>
<td>4.5</td>
<td>4.15</td>
<td>3.7</td>
<td>3.1 (p = significance as compared to other)</td>
</tr>
</tbody>
</table>

There was a 20% greater reduction in pain with combination therapy than with placebo.
No significant difference for other comparisons.
Clinical significance is in question as a difference of 1 to 1.5 on a 10-point scale is not considered clinically important

Secondary Outcomes:
All secondary outcomes scales and scores were improved with the combination treatment. There is no real way to assess the true clinical benefit from the information given. The authors claim that adding morphine to gabapentin will improve mood, reduce pain-related interference with work, sleep and enjoyment of life.

Adverse Event

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Placebo</th>
<th>Gabapentin</th>
<th>Morphine</th>
<th>Combination</th>
<th>ARI</th>
<th>NNH Placebo vs Combo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>4.7%</td>
<td>2.1%</td>
<td>38.6%</td>
<td>20.9%</td>
<td>16.7%</td>
<td>6</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0%</td>
<td>6.3%</td>
<td>4.6%</td>
<td>20.9%</td>
<td>20.9%</td>
<td>5</td>
</tr>
</tbody>
</table>

3. Will the results help me?
- Morphine dose was reduced by 10 mg per day when it was combined with the gabapentin (45 mg to 35 mg).
- Gabapentin dose was reduced from 2200 mg per day to 1700 mg per day in the combination.
- Not sure the dose differences matter clinically.
- The major surprise in this trial was that gabapentin alone was no better than placebo. This might be related to the active placebo use of lorazepam.

Conclusion: The combination of morphine + gabapentin had a small benefit in pain intensity scores as compared to either agent alone. For this small benefit, patients will have to be monitored for constipation and dry mouth.