OBJECTIVES

• Discuss the current evidence regarding opioid therapy for chronic non-cancer pain

• Describe the role of non-opioid therapy for common painful conditions

• Explain the relative risk vs. safety profiles of opioids vs. non-opioid analgesics
DISCLOSURES

• There are no real or perceived financial, litigational, or other conflicts of interest to disclose
OPIOIDS IN NON-CANCER CHRONIC PAIN
CHRONIC PAIN STATES

• Chronic pain common
  – 10% prevalence
  – Major cause of missed work
  – >25% of patients with chronic pain receive disability or injury compensation

• Co-existing depression common
FIBROMYALGIA

- Chronic condition characterized by physical and psychiatric symptoms

- Common complaints:
  - Widespread pain
  - Fatigue
  - Decreased mood/volition
  - Morning stiffness
FIBROMYALGIA

• Etiology of pain not well understood

• Proposed that pain is due to:
  – Central sensitization
  – Central disinhibition
  – Dysfunctional hypothalamic-pituitary adrenal axis
FIBROMYALGIA

• Commonly used therapies:
  – Opiates
  – NSAIDS
  – Steroids
  – Antidepressants
  – Anticonvulsants
  – Muscle relaxants

• NSAIDS, steroids not clearly beneficial
NEUROPATHY

- Chronic, painful condition

- Due to injury or disease of CNS or PNS

- Heterogeneous state of conditions
  - Diabetes
  - HIV
  - Trauma (CRPS)
NEUROPATHY: PROPOSED MECHANISMS

• Vascular
  – Advanced glycation of arterial walls
  – Ischemic proximal nerve lesion
  – Increased free radical injury
  – Nerve hypoxia
  – Epineural vessel atherosclerosis

• Metabolic
  – Various enzyme deficiencies
FIBROMYALGIA: ANTIDEPRESSANTS AND PAIN

Häuser W, Bernardy K, Uceyler N, et. Al.  JAMA; 301:198-209
FIBROMYALGIA: QUALITY OF LIFE WITH ANTIDEPRESSANTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Individuals, No.</th>
<th>Effect Size, Mean (SD)</th>
<th>Effect Size, Mean (SD)</th>
<th>SMD (95% CI)</th>
<th>Favors Treatment</th>
<th>Favors Control</th>
<th>Weight, %</th>
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<tbody>
<tr>
<td>Mean</td>
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<tr>
<td>Goldenberg et al, 1996</td>
<td>22</td>
<td>47.60 (19.80)</td>
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<td>58.50 (17.10)</td>
<td>-0.57 (-1.20 to 0.05)</td>
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<td>Goldenberg et al, 1996</td>
<td>21</td>
<td>52.30 (22.90)</td>
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<td>Heymann et al, 2001</td>
<td>37</td>
<td>39.97 (19.88)</td>
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<td>51.68 (22.90)</td>
<td>-0.54 (-1.02 to -0.06)</td>
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<td>Heymann et al, 2001</td>
<td>36</td>
<td>49.78 (21.84)</td>
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<td>51.68 (22.90)</td>
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<td>104</td>
<td>-0.36 (-0.62 to -0.09)</td>
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</table>

Test for heterogeneity: $\chi^2 = 2.35; P = .50; I^2 = 0\%$
Test for overall effect: $z = 2.61; P = .009$

<table>
<thead>
<tr>
<th>Study</th>
<th>Individuals, No.</th>
<th>Effect Size, Mean (SD)</th>
<th>Effect Size, Mean (SD)</th>
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<th>Favors Control</th>
<th>Weight, %</th>
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<td>Arnold et al, 2005</td>
<td>114</td>
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<td>Arnold et al, 2005</td>
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<td>Arnold et al, 2004</td>
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<td>Arnold et al, 2002</td>
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<td>Norregaard et al, 1995</td>
<td>21</td>
<td>0.00 (0.40)</td>
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<td>0.00 (0.40)</td>
<td>0.00 (-0.60 to 0.60)</td>
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<td>Russell et al, 2008</td>
<td>79</td>
<td>-14.77 (18.71)</td>
<td>144</td>
<td>-10.42 (17.52)</td>
<td>-0.25 (-0.53 to 0.02)</td>
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<tr>
<td>Russell et al, 2008</td>
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<td>-12.28 (17.64)</td>
<td>144</td>
<td>-10.42 (17.52)</td>
<td>-0.11 (-0.33 to 0.12)</td>
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<tr>
<td>Russell et al, 2008</td>
<td>147</td>
<td>-13.86 (17.10)</td>
<td>144</td>
<td>-10.42 (17.52)</td>
<td>-0.20 (-0.43 to 0.03)</td>
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<td>-0.31 (-0.44 to -0.18)</td>
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</table>

Test for heterogeneity: $\chi^2 = 11.16; P = .13; I^2 = 37.3\%$
Test for overall effect: $z = 4.54; P < .001$

<table>
<thead>
<tr>
<th>Study</th>
<th>Individuals, No.</th>
<th>Effect Size, Mean (SD)</th>
<th>Effect Size, Mean (SD)</th>
<th>SMD (95% CI)</th>
<th>Favors Treatment</th>
<th>Favors Control</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Overall</td>
<td>859</td>
<td></td>
<td>907</td>
<td>-0.31 (-0.42 to -0.20)</td>
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</table>

Test for heterogeneity: $\chi^2 = 13.66; P = .25; I^2 = 19.5\%$
Test for overall effect: $z = 5.59; P < .001$

Häuser W, Bernardy K, Uceyler N, et. Al. JAMA; 301:198-209
FIBROMYALGIA:
ANTIDEPRESSANTS

• SSRI’s
  – Paroxetine
  – Fluoxetine

• NSRI’s
  – Duloxetine
  – Milnacipran
NEUROPATHY: ANTIDEPRESSANTS

• Most data is for use of TCAs
  – Beneficial in most disease states except HIV
  – Cochrane: NNT 3.6 for at least moderate pain relief
• Moderate data for SNRI’s, and likely as efficacious as TCAs
• Limited data on SSRIs

Saarto T, Wiffen PJ. Cochrane Database Syst Rev. 2007; CD005454.
PREGABALIN

- GABA analog that binds to the $\alpha_2\delta$ subunit on voltage-gated calcium channels

- Beneficial in both fibromyalgia and neuropathic pain
  - Dose response
  - 150 mg daily generally ineffective
  - Most benefit from 600 mg daily
GABAPENTIN

• Exact mechanism of action unknown
• Does not bind to GABA receptor
• Structurally related to GABA

• Meta-analysis with at least moderate improvement in 43% of subjects
• Adverse events common (66%)

CARBAMAZEPINE

• Inhibit multiple channels including:
  – Na channels → hyperpolarization
  – Muscarinic/nicotinic ACh receptor
  – NMDA (glutamate) receptors
  – CNS adenosine receptor

• Metabolized to active metabolite via CYP3A4
CARBAMAZEPINE

• Numerous studies
  – Most very small and of short duration

• Meta-analysis reveals effective option for chronic neuropathic pain, but adverse effects common
  – 66% for CBZ, 27% for placebo)
NON-OPIOIDS IN THE TREATMENT OF ACUTE EXACERBATIONS OF COMMON PAINFUL CONDITIONS
CHRONIC LOW BACK PAIN

• Evidence for exercises much greater than for acute low back pain

• Meta-analysis of 38 studies found minimal role for opiates in CLBP
  – Mild efficacy, significant chance of addiction
CHRONIC LOW BACK PAIN

• NSAIDS beneficial, with maximal efficacy at 4 weeks
• No evidence to support NSAIDS in CLBP
• Cyclic antidepressants (esp. nortriptyline) beneficial
NON-OPIOIDS IN THE TREATMENT OF ACUTE PAINFUL CONDITIONS
NEPHROLITHIASIS

• Common condition:
  – Lifetime prevalence:
    • 12% for men
    • 6% for women
  – More than 2 million visits annually
NEPHROLITHIASIS: MECHANISM OF PAIN

Obstruction in ureter

↓

Hydronephrosis

↓

Pressure against Gerota's fascia

↓

Local synthesis/release of prostaglandin

Diuresis \( \uparrow \) intrarenal pressure

Ureter spasm
### NSAIDS VS. OPIATES IN NEPHROLITHIASIS: THE VAS

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>NSAIDS Mean (SD)</th>
<th>No of patients</th>
<th>NSAIDS Mean (SD)</th>
<th>Weighted mean difference (95% CI)</th>
<th>Weight (%)</th>
<th>Weighted mean difference (95% CI)</th>
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<tr>
<td>Indomethacin</td>
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<tr>
<td>Jonsson et al 1987</td>
<td>35</td>
<td>24.0 (20.0)</td>
<td>26</td>
<td>33.0 (25.0)</td>
<td>6.18 (-9.00 to -20.67 to 2.67)</td>
<td>6.18</td>
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<tr>
<td>Subtotal</td>
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<td>51</td>
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<td>11.37 (-8.73 to -17.33 to -0.12)</td>
<td>11.37</td>
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<td>Test for heterogeneity: $\chi^2=0.00$, df=1, $P=0.95$, $I^2=0%$</td>
<td>5.19</td>
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<td>Test for overall effect: $z=1.99$, $P=0.05$</td>
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<td>Diclofenac</td>
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<tr>
<td>Marthak et al 1991</td>
<td>25</td>
<td>39.1 (9.7)</td>
<td>25</td>
<td>44.6 (9.7)</td>
<td>29.11 (-5.50 to -10.88 to -0.12)</td>
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<tr>
<td>Arnau et al 1991</td>
<td>116</td>
<td>20.0 (18.0)</td>
<td>118</td>
<td>23.0 (18.0)</td>
<td>39.56 (-3.00 to -7.61 to 1.61)</td>
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<tr>
<td>Subtotal</td>
<td>141</td>
<td>143</td>
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<td>68.66 (-4.06 to -7.56 to -0.56)</td>
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<td>Test for heterogeneity: $\chi^2=0.48$, df=1, $P=0.49$, $I^2=0%$</td>
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<td>Test for overall effect: $z=2.27$, $P=0.02$</td>
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<td>Other</td>
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<td>Curry and Kelly 1995</td>
<td>17</td>
<td>26.8 (19.9)</td>
<td>24</td>
<td>26.8 (16.8)</td>
<td>6.25 0.00 (-11.60 to 11.60)</td>
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<tr>
<td>Persson et al 1985</td>
<td>47</td>
<td>17.0 (16.0)</td>
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<td>23.0 (22.0)</td>
<td>13.72 -6.00 (-13.83 to 1.83)</td>
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<td>Subtotal</td>
<td>64</td>
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<td>19.97 -4.12 (-10.61 to 2.37)</td>
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<td>Test for heterogeneity: $\chi^2=0.71$, df=1, $P=0.40$, $I^2=0%$</td>
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<td>Test for overall effect: $z=1.24$, $P=0.21$</td>
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<td>Total (95% CI)</td>
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<td>264</td>
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<td>100.00 -4.60 (-7.50 to -1.70)</td>
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<td>Test for heterogeneity: $\chi^2=2.18$, df=5, $P=0.82$, $I^2=0%$</td>
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<td>Test for overall effect: $z=3.11$, $P=0.002$</td>
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</tbody>
</table>

- Difference of 4.6 (1.7-7.5) mm favoring NSAIDS

Holdgate A, Pollock T BMJ 2004;328:1401
NSAIDS VS. OPIATES: NEED FOR RESCUE ANALGESIA

- Patients receiving NSAIDS less likely to need rescue analgesia (RR 0.75; 0.61-0.93)

Holdgate A, Pollock T BMJ 2004;328:1401
NSAIDS VS. OPIATES: INCIDENCE OF VOMITING

<table>
<thead>
<tr>
<th>Study</th>
<th>NSAIDs No/total No</th>
<th>Opioids No/total No</th>
<th>Relative risk (random) (95% CI)</th>
<th>Weight (%)</th>
<th>Relative risk (random) (95% CI)</th>
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<tr>
<td>Uden et al 1983</td>
<td>1/25</td>
<td>0/25</td>
<td>0.35 (0.18-0.49)</td>
<td>1.86</td>
<td>3.00 (0.13 to 70.30)</td>
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<tr>
<td>Persson et al 1985</td>
<td>0/48</td>
<td>3/46</td>
<td>2.14 (0.01 to 2.58)</td>
<td>2.14</td>
<td>0.14 (0.01 to 2.65)</td>
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<td>Thompson et al 1989</td>
<td>0/29</td>
<td>3/29</td>
<td>2.16 (0.01 to 2.65)</td>
<td>2.16</td>
<td>0.14 (0.01 to 2.65)</td>
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<td>Marthak et al 1991</td>
<td>0/25</td>
<td>8/25</td>
<td>2.35 (0.06 to 0.97)</td>
<td>2.35</td>
<td>0.06 (0.00 to 0.97)</td>
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<td>Cordell et al 1984</td>
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<td>5.23 (0.10 to 4.22)</td>
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<td>0.65 (0.10 to 4.22)</td>
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<td>Lundstam 1982</td>
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<td>3/32</td>
<td>7.93 (0.20 to 4.33)</td>
<td>7.93</td>
<td>0.94 (0.20 to 4.33)</td>
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<td>Sommer et al 1989</td>
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<td>8.41 (0.06 to 1.17)</td>
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<td>0.27 (0.06 to 1.17)</td>
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<td>Lehtonen et al 1983</td>
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<td>0.68 (0.16 to 2.98)</td>
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<td>Oosterlinck et al 1990</td>
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<td>13.47 (0.09 to 0.90)</td>
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<td>0.28 (0.09 to 0.90)</td>
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<td>Arnaud et al 1991</td>
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<td>47.98 (0.16 to 0.55)</td>
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<tr>
<td>Total (95% CI)</td>
<td>445</td>
<td>380</td>
<td>100.00 (0.23 to 0.53)</td>
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</table>

Total events: 26 (NSAIDs), 74 (opioids)

Test for heterogeneity: $\chi^2=7.58$, df=9, $P=0.58$, $I^2=0\%$

Test for overall effect: $z=4.84$, $P=0.0001$

- **RR = 0.35 (0.18-0.49)**

Holdgate A, Pollock T BMJ 2004;328:1401
OPIATES AND NSAIDS

• Limited number of studies with 3 arms

• Addition of opiates to NSAIDS has been shown to result in:
  – Decreased pain
  – Possibly increase side effects

α ANTAGONISTS

- Inhibit ureteral musculature contractions
- Reduce basal tone
- Decreased peristaltic frequency and colic pain

- Demonstrated to reduce analgesic requirements, colic episodes, and need for hospital admission
<table>
<thead>
<tr>
<th></th>
<th>α-Blocker</th>
<th>Control</th>
<th>( p ) value</th>
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<tbody>
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<td>Analgesic requirements</td>
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<tr>
<td>Autorino, 2005 [25]</td>
<td>0.003</td>
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<tr>
<td>Ayubov, 2007 [36]</td>
<td>&lt;0.0001</td>
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<tr>
<td>Dellabella, 2003 [20]</td>
<td>&lt;0.0001</td>
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<td>Dellabella, 2005 [28]</td>
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<td>De Sio, 2006 [29]</td>
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<td>Han, 2006 [33]</td>
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<td>Kim, 2006 [34]</td>
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<td>Mohseni, 2006 [31]</td>
<td>Analgesic</td>
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<tr>
<td>Poppiglia, 2004 [21]</td>
<td>were lower for</td>
<td>&lt;0.0001</td>
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<tr>
<td>Poppiglia, 2006 [30]</td>
<td>all α-blocker</td>
<td>&lt;0.001</td>
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<tr>
<td>Poppiglia, 2008 [40]</td>
<td>studies compared</td>
<td>n.s.</td>
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<tr>
<td>Sayed, 2008 [41]</td>
<td>to controls</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Shaaban, 2008 [56]</td>
<td>&lt;0.05</td>
<td></td>
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</tr>
<tr>
<td>Wang, 2008 [45]</td>
<td>&lt;0.001</td>
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<tr>
<td>Bhagat, 2007 (SWL) [54]</td>
<td>0.3</td>
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<tr>
<td>Gravas, 2007 (SWL) [55]</td>
<td>0.02</td>
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<td></td>
</tr>
<tr>
<td>Gravina, 2005 (SWL) [55]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han, 2006 (SWL) [33]</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mukhtarov, 2007 (SWL) [38]</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colic episodes (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perron, 2008 [39]</td>
<td>7.94</td>
<td>7.89</td>
<td>n.s.</td>
</tr>
<tr>
<td>Poppiglia, 2008 [40]</td>
<td>1.4</td>
<td>1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Resim, 2005 [24]</td>
<td>2</td>
<td>2.5</td>
<td>0.038</td>
</tr>
<tr>
<td>Sayed, 2008 [41]</td>
<td>1.5</td>
<td>2.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Resim, 2005 (SWL) [24]</td>
<td>0</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Wang, 2008 (SWL) [69]</td>
<td>5</td>
<td>20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hospitalisation (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autorino, 2005 [25]</td>
<td>9</td>
<td>21</td>
<td>0.01</td>
</tr>
<tr>
<td>Dellabella, 2003 [20]</td>
<td>0</td>
<td>33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dellabella, 2005 [28]</td>
<td>1.4</td>
<td>34.3</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>De Sio, 2006 [29]</td>
<td>10</td>
<td>27.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Erturhan, 2007 [35]</td>
<td>3.3</td>
<td>6.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Work days lost</td>
<td>Dellabella, 2005 [25]</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

n.s. = not significant; SWL = shock wave lithotripsy.
MIGRAINES

• Affect 15% of population
• 3.4 million annual ED visits for headache

• Non-opioid options:
  – NSAIDS
  – Triptans
  – Phenothiazines
  – Dihydroergotamines
  – Propofol
  – Ketamine
  – Calcitonin gene related peptide (CGRP)
MIGRAINE: PATHOPHYSIOLOGY

- Historically felt to be vascular
  - Aura due to vasoconstriction
  - Headache due to vasodilation

- New theory involves activation of trigeminovascular system
TRIGEMINOVASCULAR SYSTEM

- Pseudounipolar sensory neurons originate from trigeminal ganglion

- Stimulation of trigeminal ganglion releases vasoactive peptides
  - Substance P
  - Calcitonin Gene Related Peptide (CGRP)
  - Neurokinin A
CALCITONIN GENE RELATED PEPTIDE

- CGRP is a neuropeptide expressed in trigeminal ganglia nerves
- CGRP causes vasodilation of cerebral and dural vessels
- Infusion of CGRP induces migraines
CALCITONIN GENE RELATED PEPTIDE

- Most widely studied GCRP antagonists
  - Telcagepant
  - Olcegepant

- Appear to be at least as effective as triptans and superior to placebo

- Not yet FDA approved
CALCITONIN GENE RELATED PEPTIDE

• Prophylactic therapy:
  - Telcagepant bid x 3 months resulted in higher rates of transaminitis
  - 4/09 Merck announced they would not be seeking a New Drug Application

• Merck Research Laboratories withdrew MK-3207, another CGRP receptor antagonist
CURRENT TREATMENT PRACTICES

• Use of opiates for migraines varies substantially (16-71%) in US EDs

• Treatments rendered
  – Dopamine antagonists (68%)
  – Opiates (64%)
  – NSAIDS (33%)
  – Migraine-specific medications (<10%)
NSAIDS, APAP

- APAP less potent than ASA
- Comparing APAP to ketorolac;
  - 57% of patients with no-mild pain at 2h after 400 mg of ibuprofen
  - NNT for ibuprofen 3-7; 5-12 for APAP
- ASA and NSAIDS have efficacy similar to oral sumatriptan
OPIATES

- Meperidine less effective and associated with more side effects than most other opiates

- Superior to low dose NSAIDS; less effective than phenothiazines or ergotamines

- Risk of dependence, chronic migraines
TRIPTANS

• Provide agonism at 5HT\textsubscript{1D} and 5HT\textsubscript{1B}
• Results in vasoconstriction of basilar artery and vessels in dura matter

• Primary contraindications include:
  – CV disease
  – Basilar/hemiplegic migraine
  – Use ergotamine (24 hours)
ERGOTAMINE

• DHE activates
  – $5HT_{1B, 1D}$ (as do triptans)
  – $5HT_{1A, 1F}$ and $5HT_{2A, 2C}$ and $D_{1, 2}$
  – Inhibits prostaglandin release from glia → prevents trigeminal nucleus caudalis activation

• Same contraindications as triptans, but can cause serotonin syndrome
EFFICACY

• Cochrane review: ergotamine + caffeine less effective than sumatriptan

McCrorry DC, Gray RN. Cochrane Database Syst Rev. 2003; 3:CD002915
PHENOTHIAZINES

Table 5.—Forest Plot of Phenothiazines vs Placebo for Clinical Success

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Placebo</th>
<th>Phenothiazine</th>
<th>Odds ratio (nonevent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, random, 95% CI</td>
</tr>
<tr>
<td>Bilgai et al 2002</td>
<td>9</td>
<td>60 56</td>
<td>26.44 [10.29-67.96]</td>
</tr>
<tr>
<td>Coppola et al 1995</td>
<td>7</td>
<td>24 18</td>
<td>16.93 [2.71-44.14]</td>
</tr>
<tr>
<td>Jones et al 1989</td>
<td>18</td>
<td>40 37</td>
<td>9.04 [2.94-27.79]</td>
</tr>
<tr>
<td>Jones et al 1986</td>
<td>4</td>
<td>29 12</td>
<td>4.69 [1.29-17.10]</td>
</tr>
<tr>
<td>McEwen 1987</td>
<td>4</td>
<td>17 9</td>
<td>2.92 [0.69-12.32]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>170</td>
<td>179 100.0%</td>
<td>8.92 [4.08-10.51]</td>
</tr>
</tbody>
</table>

Total events: 42 132
Heterogeneity: Tau² = 0.41; Chi² = 8.25, d.f. = 4 (P = .04); I² = 52%
Test for overall effect: Z = 5.48 (P < .00001)

Table 6.—Forest Plot of Phenothiazines vs Active Agents for Clinical Success

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Active agent</th>
<th>Phenothiazine</th>
<th>Odds ratio (nonevent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>M-H, random, 95% CI</td>
</tr>
<tr>
<td>Cameron et al 1995</td>
<td>29</td>
<td>44 37</td>
<td>1.91 [0.75-4.88]</td>
</tr>
<tr>
<td>Coppola et al 1995</td>
<td>12</td>
<td>24 18</td>
<td>3.00 [0.88-10.18]</td>
</tr>
<tr>
<td>Friedman et al 2008</td>
<td>29</td>
<td>38 32</td>
<td>1.42 [0.47-4.30]</td>
</tr>
<tr>
<td>Jones et al 1996</td>
<td>6</td>
<td>29 12</td>
<td>2.88 [0.89-9.26]</td>
</tr>
<tr>
<td>Kelly et al 1997</td>
<td>19</td>
<td>20 22</td>
<td>1.16 [0.07-19.80]</td>
</tr>
<tr>
<td>Laine et al 1998</td>
<td>15</td>
<td>22 22</td>
<td>5.13 [0.93-26.18]</td>
</tr>
<tr>
<td>Sem et al 1998</td>
<td>29</td>
<td>35 25</td>
<td>1.29 [0.33-5.11]</td>
</tr>
<tr>
<td>Shrestha et al 1996</td>
<td>14</td>
<td>15 13</td>
<td>0.46 [0.04-5.75]</td>
</tr>
<tr>
<td>Stillet et al 1991</td>
<td>27</td>
<td>37 26</td>
<td>0.86 [0.03-2.41]</td>
</tr>
<tr>
<td>Tanen et al 2003</td>
<td>4</td>
<td>19 15</td>
<td>11.25 [2.52-50.27]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>283</td>
<td>266 100.0%</td>
<td>2.04 [1.25-3.31]</td>
</tr>
</tbody>
</table>

Total events: 184 222
Heterogeneity: Tau² = 0.14; Chi² = 11.85, d.f. = 9 (P = .22); I² = 24%
Test for overall effect: Z = 2.87 (P = .004)

Kelly AM, Walcynski T, Gunn B. Headache. 2009; 49:1324
PHENOTHIAZINES: EFFICACY

• Incidence of orthostasis quite low with prophylactic intravenous fluids

• With prophylactic IVF, chlorpromazine is superior to ergot derivatives or meperidine and similar to ketorolac, metoclopramide, and sumatriptan

• Limited data on PO administration
KETAMINE AND MIGRAINE

• Antagonist of the NMDA receptor

• NMDA receptor mediated plasticity in chronic pain

• Emerging data on analgesic benefits of sub dissociative doses in several painful conditions
• 17 migraine suffers
• 80 mcg/kg SQ vs. saline for acute pain
  - Favors ketamine
• Randomized, double-blind cross over for chronic pain with 80 mcg/kg SQ tid vs. saline → strongly favors ketamine
PROPOFOL AND MIGRAINE
PROPOFOL AND MIGRAINE

• Numerous case reports and small case series with benefit

• Largest study to date:
  - 77 patients with refractory migraine
  - 20-30 mg bolus q3-5 min
  - Mean dose 110 mg
  - 63 (82%) with complete resolution of HA
  - 14 (18%) with 50-90% improvement
SCIATICA: NSAIDS, OPIATES

• NSAIDS superior to placebo

• Equivalent to acetaminophen, but associated with more side effects

• All NSAIDS, including selective COX-2 inhibitors equally effective

• Opiates may be beneficial for acute pain; benefit in chronic pain questionable

SCIATICA: STEROIDS

• No benefit from steroid administration
“MUSCLE RELAXANTS”

• Some evidence supporting carisoprodol, cyclobenzaprine, orphenadrine, or tizanidine compared with placebo

• Poor data supporting metaxalone, metocarbamol, baclofen vs. placebo

• Insufficient data comparing efficacy

SAFETY VS. RISK OF OPIATES VS. NON-OPIATES
DEPENDENCE/ADDICTION

• Most opiates have ability to cause dependence and associated with abuse
  • Well known withdrawal syndrome
  • Tramadol exception
• SSRIs, SNRIs, TCA associated with potential withdrawal syndrome but low abuse potential
TRAMADOL: ADVERSE EVENTS

• Most adverse events involve GI or CNS

• Anorexia, fatigue, constipation more likely in those > 65 years,

• AE most likely with CR or ER formulations

• Seizures possible
GABAPENTIN

• Two-thirds of patients taking 1200+ mg gabapentin for neuropathy develop at least one adverse event (vs. 51% placebo)
  – Adverse events result in 12% withdrawal rate from studies (RR 1.36; 1.09-1.71)
  – Dizziness, somnolence, peripheral edema

PREGABALIN

• Pregabalin associated with dizziness, ataxia, visual changes, confusion

• NNT: 5   NNH: 11

LONG TERM USE OF NSAIDS: CV ADVERSE EVENTS

• CV events:
  – Greatest rate of MI: Rofecoxib (RR 2.12; 1.26-3.56)
  – Greatest rate of CVA: Ibuprofen (RR 3.36; 1-11.6)

LONG TERM USE OF NSAIDS: GI ADVERSE EVENTS

- Pooled risk of UGIB after NSAIDS 3.8 (3.6-4.1)
- Dose response
- Minimal variation in risk between individual NSAIDS when compatible doses considered

ANTIDEPRESSANT ADVERSE EVENTS:

• TCA’s associated with orthostasis and antimuscarinic symptoms

• SSRI’s mostly associated with GI illness

• Discontinuation syndrome
CARBAMAZAPINE: ADVERSE EVENTS

• Somnolence/dizziness reported in > 50% of subjects taking CBZ

• Rare, but serious adverse events:
  – SIADH
  – SJS
  – Bone marrow suppression
  – Anticonvulsant Hypersensitivity Syndrome (AHS)
CONCLUSIONS

• Opiate use is common, but not always the most appropriate therapy

• Various antidepressants (e.g. TCA’s, SNRI’s) and some anticonvulsants may be effective in treating chronic painful conditions
CONCLUSIONS

• NSAIDS, alpha antagonists should be used for treatment of nephrolithiasis

• Acute migraine headaches can be treated with phenothiazines, NSAIDS, triptans, and ergotamines
  – Ketamine and propofol in future?
THANK YOU!

THANK YOU!