Duloxetine for the Management of Chronic Pain

Eli Lilly and Company
<table>
<thead>
<tr>
<th>Agenda</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Introduction</strong></td>
</tr>
<tr>
<td>Michael Robinson, MD</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
</tr>
<tr>
<td>Indianapolis, IN</td>
</tr>
<tr>
<td><strong>Disease State</strong></td>
</tr>
<tr>
<td>Daniel J. Clauw MD</td>
</tr>
<tr>
<td>Professor of Anesthesiology, Medicine, and Psychiatry</td>
</tr>
<tr>
<td>The University of Michigan</td>
</tr>
<tr>
<td><strong>Efficacy and Safety of Duloxetine</strong></td>
</tr>
<tr>
<td>Vladimir Skljarevski, MD</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
</tr>
<tr>
<td><strong>Hepatic Safety of Duloxetine</strong></td>
</tr>
<tr>
<td>Arie Regev, MD</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
</tr>
<tr>
<td><strong>Population Based Data and Risk Management Plan</strong></td>
</tr>
<tr>
<td>Stephen Knowles, MD</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
</tr>
<tr>
<td><strong>Benefit Risk Assessment</strong></td>
</tr>
<tr>
<td>Daniel J. Clauw MD</td>
</tr>
<tr>
<td><strong>Sponsor Conclusion and Closing</strong></td>
</tr>
<tr>
<td>Michael Robinson, MD</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
</tr>
</tbody>
</table>
Duloxetine Approved Indications and Chronic Pain Development

- Representative pain conditions to complement DPNP & FM
  - 1 positive study required in Chronic Pain due to Osteoarthritis
  - 1 positive study required in Chronic Low Back Pain

Abbreviations:  DPNP = diabetic peripheral neuropathic pain, FM = fibromyalgia, GAD = generalized anxiety disorder, MDD = major depressive disorder
Duloxetine is indicated for the management of chronic pain of at least moderate severity in adults who require daily treatment for an extended period of time.

Chronic pain conditions that were studied include DPNP, FM, chronic pain due to OA, and CLBP.

Duloxetine has not been studied in chronic visceral pain or neuropathic pain due to central nervous system lesions.
Research Conclusions for Duloxetine

♦ Duloxetine is a centrally acting analgesic
  • Selective 5-HT and NE reuptake inhibition
  • Mechanism different from opioids and NSAIDs

♦ Demonstrated efficacy across representative types of chronic pain (DPNP, FM, OA, CLBP)

♦ Overall safety data in CLBP and OA similar to that observed in prior approved indications
Overview of Chronic Pain

Daniel J. Clauw M.D.

Professor of Anesthesiology, Medicine (Rheumatology) and Psychiatry
Director, Chronic Pain and Fatigue Research Center
The University of Michigan
Overview

- Chronic pain states often “mixed” pain states
  - Subset of individuals displaying augmented CNS pain processing (diffuse hyperalgesia)

- Modifications of current treatment paradigms needed
  - Inclusion of CNS contribution to pain

- Duloxetine
  - Different MOA
  - Centrally-acting analgesic
  - May have favorable benefit:risk profile compared to other available treatment options
Chronic Pain

- Chronic Pain affects >45 million Americans and can be a major cause of work absenteeism, underemployment, and unemployment\(^1,2\)
  - The most common reason for medical appointments and costs the US over $100 billion in health care and lost productivity\(^3\)
  - Leading cause of disability in the working-age population\(^4\)
- Many populations with chronic pain receive no or improper treatment\(^3\)

## Mechanistic Characterization of Pain

<table>
<thead>
<tr>
<th>Peripheral damage or inflammation</th>
<th>Neuropathic</th>
<th>Central, non-neuropathic, non-inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primarily due to inflammation or mechanical damage in periphery</td>
<td>• Damage or entrapment of peripheral nerves</td>
<td>• Augmented CNS pain and processing (i.e. diffuse hyperalgesia)</td>
</tr>
<tr>
<td>• NSAID, opioid responsive</td>
<td>• Responds to both peripheral and centrally acting analgesics</td>
<td>• NSAID, opioid non-responsive; respond to TCAs and other centrally acting analgesics</td>
</tr>
<tr>
<td>• Responds to procedures that correct underlying “problem”</td>
<td>• Responds to surgery to relieve nerve compression (if present)</td>
<td>• Surgery ineffective</td>
</tr>
<tr>
<td>• Classic examples</td>
<td>• Classic examples</td>
<td>• Classic examples</td>
</tr>
<tr>
<td>• Acute pain</td>
<td>• Neuropathic low back pain</td>
<td>• Fibromyalgia</td>
</tr>
<tr>
<td>• Osteoarthritis</td>
<td>• DPNP</td>
<td>• IBS</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
<td></td>
<td>• TMJD</td>
</tr>
<tr>
<td>• Cancer pain</td>
<td></td>
<td>• Interstitial cystitis</td>
</tr>
</tbody>
</table>
Neural Influences on Pain and Sensory Processing

**Facilitation**
- Substance P $\uparrow$
- Glutamate and EAA $\uparrow$
- Serotonin $(5HT_{2a, 3a})$ $\uparrow$
- Nerve growth factor $\uparrow$

**Inhibition**
- Descending anti-nociceptive pathways
- Norepinephrine-serotonin $(5HT_{1a,b})$, dopamine $\downarrow$
- Opioids $\uparrow$
- GABA
- Cannabinoids
- Adenosine

Adapted from Schmidt-Wilcke T and Clauw DJ. Pharmacology & Therapeutics. 2010:127(3); 283-294.
Pain Sensitivity in General Population

- Like most physiological processes, we have a “volume control” setting for how brain and spinal cord processes pain.

- Likely set by genes we are born with, and modified by neuro-hormonal factors and neural plasticity.

- The higher the volume control setting, the more pain we will experience, irrespective of peripheral nociceptive input.

Conditions Characterized by Augmented CNS Processing of Pain

- Fibromyalgia
- Temporomandibular disorder\(^1,^2\)
- Irritable bowel syndrome\(^3,^4\)
- Headache (tension > migraine)\(^5,^6\)
- Idiopathic low back pain\(^7,^8\)
- Rheumatoid arthritis\(^9\)
- Osteoarthritis\(^10\)

Other Non-Traditional Broad Spectrum Analgesics Have SNRI Activity

• **Tramadol**¹,²
  - Broad efficacy across a number of chronic pain states
  - Not clear whether SNRI or opioid activity leads to analgesia
  - Opioidergic safety concerns

• **Tricyclic antidepressants**³,⁴
  - Broad efficacy in a number of chronic pain states
  - Use in clinical practice limited due to side effects
    - Severe - cardiac conduction problems, narrow therapeutic index
    - Anticholinergic and antihistaminergic tolerability

---

Osteoarthritis of the Knee

- Historically a classic peripheral pain syndrome, but poor relationship between structural abnormalities and symptoms.¹
  - 30-40% of patients with Grade 3/4 K/L radiographic OA have no symptoms
  - 10% of patients with severe pain have normal radiographs
- Psychological factors explain very little of variance between symptoms and structure²
- Nociception important within individual with OA³
- Subsets of patients with OA of the knee display hyperalgesia and attenuated DNIC ⁴
- Several studies show genetic factors related to catecholamine breakdown (Catechol-O-methyl transferase [COMT] gene) predict the presence and severity of pain⁵,⁶

Chronic Low Back Pain (CLBP)

• Well known poor relationship between structural abnormalities and pain
• Several studies have demonstrated diffuse hyperalgesia at neutral sites in individuals with idiopathic chronic low back pain \(^1,2\)
  • One study showed that pain sensitivity at thumb was a greater predictor of pain and functional status than X-ray/MRI of back or psychological factors\(^1\)
• Functional MRI studies have demonstrated central pain augmentation very similar to that seen in fibromyalgia\(^2\)
• GCH1 haplotype predicts decreased pain following discectomy\(^3\)

Efficacy and Safety of Duloxetine in Chronic Pain

Vladimir Skljarevski, MD
Eli Lilly and Company
## Overview

- **Efficacy across chronic pain types**
  - Focus on CLBP and OA
- **Dose recommendation**
- **General safety review**
# Duloxetine Chronic Pain Disease Models

- **Neuropathic pain (DPNP)**
  - 3 studies

- **Central/Non-neuropathic/non-inflammatory pain (FM)**
  - 4 studies

- **Mixed type of pain (CLBP)**
  - 3 studies

- **Inflammatory/joint-related pain (OA)**
  - 2 studies
Duloxetine DPNP Studies: Cumulative Improvement in Pain from Baseline (BOCF)

Cumulative % of Improvement in Average Pain Score

![Graph showing cumulative improvement in average pain score for Duloxetine (DLX) at 60mg and 120mg doses compared to placebo (PBO)].

- DLX 60 (N=112)
- DLX 120 (N=109)
- PBO (N=111)

![Another graph showing similar data for DPNP-AVa].

- DLX 60 (N=110)
- DLX 120 (N=111)
- PBO (N=106)
Duloxetine FM Studies: Cumulative Improvement in Pain from Baseline (BOCF)

Cumulative % of Improvement in Average Pain Score

FM-CA

- DLX 60 (N=118)
- DLX 120 (N=116)
- PBO (N=120)

FM-CJ

- DLX 20 (N=79)
- DLX 60 (N=150)
- DLX 120 (N=147)
- PBO (N=144)
Study Overview
CLBP and OA Studies

♦ Study Designs
  • 12 to 13 week study duration
  • Approx. 115 patients/arm
  • Duloxetine 60 and 120 mg/day

♦ Protocol Specified Outcomes
  • Primary outcome: Average pain severity (0-10 scale)
  • Key secondary outcomes
    – Patient Global Impression of Improvement (PGI-I)
    – Disease specific physical function (RMDQ, WOMAC)
Starting dose of duloxetine was 30 mg for 1 week in all studies except CLBP-GC.
Statistical Methods per Protocol
CLBP and OA Studies

♦ Primary Endpoint Analysis
  • Mixed-effects model repeated measures (MMRM)

♦ Secondary Endpoints Analysis
  • Last observation carried forward (LOCF)

♦ Sensitivity Analysis
  • Baseline observation carried forward (BOCF)
Key Entry Criteria
CLBP and OA Studies

♦ CLBP
  • Adults ≥ 18 years with non-radicular low back pain (Quebec Class I or II) present on most days for ≥ 6 mo

♦ OA
  • Adults ≥ 40 years with OA of knee (ACR clinical & radiographic criteria), pain ≥ 14 days/mo for 3 mo

♦ Average Pain Severity ≥ 4 (0-10 scale)

♦ NSAIDs/Acetaminophen: ongoing stable dose allowed*

♦ Exclusion: major depressive disorder (MDD)

*Ongoing NSAID/Acetaminophen use not allowed in CLBP-GC
## Baseline Characteristics

### CLBP and OA Studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean yr)</td>
<td>54</td>
<td>51</td>
<td>54</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>Gender, Female (%)</td>
<td>61</td>
<td>61</td>
<td>57</td>
<td>77</td>
<td>65</td>
</tr>
<tr>
<td>Ethnicity, Caucasian (%)</td>
<td>95</td>
<td>75</td>
<td>80</td>
<td>98</td>
<td>84</td>
</tr>
<tr>
<td>Average Pain Severity (mean)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Duration of Pain (yr)</td>
<td>9</td>
<td>9</td>
<td>12</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>
## Patient Disposition

**CLBP and OA Studies**

<table>
<thead>
<tr>
<th></th>
<th>CLBP-GC</th>
<th></th>
<th></th>
<th>CLBP-EN</th>
<th></th>
<th></th>
<th>CLBP-EO</th>
<th></th>
<th></th>
<th>OA-FG</th>
<th></th>
<th></th>
<th>OA-EP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>DLX</td>
<td>PBO</td>
<td></td>
<td>DLX</td>
<td>PBO</td>
<td></td>
<td>DLX</td>
<td>PBO</td>
<td></td>
<td>DLX</td>
<td>PBO</td>
<td></td>
<td>DLX</td>
<td>PBO</td>
<td></td>
</tr>
<tr>
<td>198</td>
<td>203</td>
<td></td>
<td></td>
<td>115</td>
<td>121</td>
<td></td>
<td>287</td>
<td>117</td>
<td></td>
<td>128</td>
<td>128</td>
<td></td>
<td>111</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>Completed, %</td>
<td>74</td>
<td>77</td>
<td></td>
<td>73</td>
<td>81</td>
<td></td>
<td>64*</td>
<td>70</td>
<td></td>
<td>73*</td>
<td>87</td>
<td></td>
<td>69</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Reason for discontinuation</td>
<td>Adverse Event, %</td>
<td>15*</td>
<td>5</td>
<td>14*</td>
<td>6</td>
<td>18*</td>
<td>9</td>
<td>19*</td>
<td>5</td>
<td>14</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of efficacy, %</td>
<td>1*</td>
<td>4</td>
<td></td>
<td>3</td>
<td>4</td>
<td></td>
<td>4</td>
<td>5</td>
<td></td>
<td>1</td>
<td>4</td>
<td></td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Any other reason, %</td>
<td>10</td>
<td>13</td>
<td></td>
<td>13</td>
<td>12</td>
<td></td>
<td>17</td>
<td>16</td>
<td></td>
<td>8</td>
<td>4</td>
<td></td>
<td>15</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

*p<.05 vs PBO
CLBP-EO includes the 20 mg dose
CLBP-EN reflects 13-week study period
CLBP-GC Study
Average Pain Severity

Primary Outcome: BPI Average Pain Severity
12-Wk Fixed-Dose Study

BOCF

*p=.004 (BOCF)

MMRM

Weeks on Treatment

LS Mean Change (BOCF)

* DLX 60 (N=198)
* PBO (N=203)

LS Mean Change (MMRM)

* p<.05 vs PBO
Primary Outcome: BPI Average Pain Severity
13-Wk Dose Escalation Study

**BOCF**

*p=.019 (BOCF)*

**MMRM**

Weeks on Treatment

LS Mean Change (BOCF)

-3.5
-3
-2.5
-2
-1.5
-1
-0.5
0

LS Mean Change (MMRM)

-3.5
-3
-2.5
-2
-1.5
-1
-0.5
0

- DLX 60/120 (N=109)
- PBO (N=115)

60/120 mg

*p<.05 vs PBO*
Primary Outcome: Weekly 24-Hr Average Pain Severity
13-Wk Fixed-Dose Study

BOCF

p=.228 (BOCF)

MMRM

Weeks on Treatment

*\(p<.05\) vs PBO
Primary Outcome: BPI Average Pain Severity
13-Wk Dose Escalation Study

BOCF

*\( p = .013 \) (BOCF)

MMRM

Weeks on Treatment

LS Mean Change (MMRM)

-3.5
-3.0
-2.5
-2.0
-1.5
-1.0
-0.5
0

DLX 60/120 (N=121)
PBO (N=127)

*\( p < .05 \) vs PBO

60/120 mg
OA-EP Studies
Average Pain Severity

Primary Outcome: Weekly 24-Hr Average Pain Severity
13-Wk Dose Re-Randomization Study

BOCF

p=.086 (BOCF)

MMRM

Weeks on Treatment

- DLX 60 (N=111)
- PBO (N=120)

*p<.05 vs PBO

LS Mean Change (MMRM)

- DLX 60/120 (N=108)
- PBO (N=119)

*5877.01
## Overview of Efficacy Results in CLBP and OA (BOCF)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Average Pain Severity</th>
<th>PGI-I</th>
<th>Physical Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLBP-GC</td>
<td>p=.004</td>
<td>p=.003</td>
<td>p=.073</td>
</tr>
<tr>
<td>CLBP-EN</td>
<td>p=.019</td>
<td>p=.001</td>
<td>p=.042</td>
</tr>
<tr>
<td>OA-FG</td>
<td>p=.013</td>
<td>p=.074</td>
<td>p=.149</td>
</tr>
<tr>
<td>CLBP-EO (60 mg)</td>
<td>p=.228</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OA-EP</td>
<td>p=.086</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Physical Function Scales: CLBP = RMDQ, OA = WOMAC Physical Function Subscale
Duloxetine 60 mg: Efficacy in CLBP/OA Studies, Average Pain Severity (BOCF)

Fixed-Dose Study

**CLBP-GC**

Flexible-Dose Studies

**CLBP-EN**  
**OA-FG**

Analysis: Patients who were non-responders at wk 7 were treated as early discontinuations.

*p<.05 vs PBO*
Average Pain Severity
Duloxetine Effect Size at 3 Months
Duloxetine
Safety and Tolerability
Summary of Risks

- Risks characterized in current label
  - e.g., suicidality, hepatic, bleeding, cardiovascular
- No new safety issues identified in new populations studied
- Ongoing risk management plan
## Duloxetine Safety Analyses

### Description of Key Datasets

<table>
<thead>
<tr>
<th>Placebo-Controlled Studies Datasets&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Duloxetine Patients (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ 4 OA/CLBP Studies</td>
<td>641</td>
</tr>
<tr>
<td>♦ Other Placebo-Controlled Studies</td>
<td></td>
</tr>
<tr>
<td>• MDD, GAD, SUI/LUTD, DPNP, FM</td>
<td></td>
</tr>
<tr>
<td>♦ All Placebo-Controlled Studies</td>
<td>10,326</td>
</tr>
</tbody>
</table>

### Overall Exposures

- ♦ All Study Exposures<sup>b</sup> 29,237
- ♦ Post-Marketing Exposures (approx 70% in US)<sup>c</sup> 29.9 million

### Population Based / Retrospective Cohort Studies

- ♦ i3 Hepatic Studies (n=2) 35,121
- ♦ i3 Cardiovascular Study 21,457
- ♦ Pharmetrics Suicidality Study 13,541

---

<sup>a</sup>Excludes CLBP-GC,  
<sup>b</sup>As of 20 November 2008,  
<sup>c</sup>As of 02 May 2010
### Duloxetine Exposures by Dose and Duration in All Duloxetine Studies

<table>
<thead>
<tr>
<th></th>
<th>Any Exposures</th>
<th>≥6 months</th>
<th>≥12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Patient Years</td>
<td>n</td>
</tr>
<tr>
<td><strong>OA/CLBP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mg</td>
<td>565</td>
<td>168.8</td>
<td>86</td>
</tr>
<tr>
<td>120 mg</td>
<td>264</td>
<td>71.1</td>
<td>41</td>
</tr>
<tr>
<td><strong>All Pain Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mg</td>
<td>2,876</td>
<td>750.1</td>
<td>490</td>
</tr>
<tr>
<td>90 mg</td>
<td>53</td>
<td>18.4</td>
<td>12</td>
</tr>
<tr>
<td>120 mg</td>
<td>2,457</td>
<td>1,411.7</td>
<td>1,281</td>
</tr>
<tr>
<td><strong>All Studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mg</td>
<td>12,963</td>
<td>2,638.1</td>
<td>1,143</td>
</tr>
<tr>
<td>80 mg</td>
<td>12,830</td>
<td>7,801.7</td>
<td>4,772</td>
</tr>
<tr>
<td>90 mg</td>
<td>2,595</td>
<td>649.5</td>
<td>377</td>
</tr>
<tr>
<td>120 mg</td>
<td>5,382</td>
<td>2,656.2</td>
<td>2,230</td>
</tr>
</tbody>
</table>

Data for doses less than 60 mg not included in this table.
### Overall Safety Event Profile

**Chronic Pain Placebo-Controlled Studies**

| Event | OA/CLBP | | | FM | | | DPNP | |
|-------|---------|---|---|---|---|---|---|
|       | DLX (N=641) | PBO (N=486) | DLX (N=876) | PBO (N=535) | DLX (N=906) | PBO (N=448) |
| Deaths, n | 0 | 0 | 0 | 0 | 1 | 1 |
| Any SAE, % | 2.2 | 1.6 | 2.4 | 2.1 | 3.1 | 3.8 |
| DC - Any AE, % | 16.8* | 6.4 | 19.6* | 11.8 | 12.9* | 5.1 |
| Any TEAE , % | 61.0* | 45.1 | 89.0* | 80.0 | 80.7* | 70.1 |

Note: one patient death due to cardiopulmonary arrest occurred 11 days post discontinuation in CLBP-EO study.

- DC due to AEs in ≥1% of duloxetine-treated patients:
  - OA/CLBP: nausea*, insomnia
  - FM: nausea, insomnia, somnolence*, fatigue
  - DPNP: nausea*, dizziness, somnolence*

* p<.05 vs PBO
### Most Common TEAEs in Chronic Pain Placebo-Controlled Studies

<table>
<thead>
<tr>
<th>Event</th>
<th>OA/CLBP</th>
<th>FM</th>
<th>DPNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Insomnia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dizziness</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Agitation</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

- **TEAEs:** Generally transient, mild/moderate in severity, and occur early
- **No new TEAE safety signals seen in the 9-mo extension of CLBP-EN**
Five Most Frequent TEAEs Over Time
All Duloxetine Studies

- Nausea
- Headache
- Dry Mouth
- Constipation
- Insomnia

Incidences Over Time:

- 1-6 months (5483.1)
- 7-12 months (2910.5)
- 13-18 months (1234.4)
- 19-24 months (655.0)
- >24 months (1307.1)
Suicidal Ideation/Behavior with Duloxetine
All Placebo-Controlled Studies

♦ Results from 2006 retrospective analysis of all duloxetine placebo-controlled trials were consistent with FDA suicide meta-analysis of antidepressants
  • In patients with psychiatric disorders:
    – <25 years: small increased risk
    – 25-64 years: no increased risk
    – >65 years: reduced risk

♦ CLBP and OA studies
  • No cases of suicidal ideation/behavior in acute, placebo-controlled period
    – 1 case of suicidal ideation in the extension period of CLBP-EN
5.5 Abnormal Bleeding

SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.
Bleeding Events
All Placebo-Controlled Studies

* p<.05 vs placebo

Percent of Patients with ≥1 TEAE

- Any Bleeding
  - DLX (N=10,326): 1.83%
  - PBO (N=7,496): 1.27%

- GI Bleeding
  - DLX (N=10,326): 0.23%
  - PBO (N=7,496): 0.16%
Incidence of GI Bleeding Events Steady Over Time in All Duloxetine Studies
Bleeding Events in Patients Using NSAIDs/Aspirin All Placebo-Controlled Studies

No statistical significant difference between DLX vs PBO
NSAIDs/Aspirin use = aspirin or other NSAIDs (including Cox-2) during treatment period
Changes in Sitting Diastolic and Systolic BP in Long-Term Duloxetine Exposures, All Indications

LS Mean Change mm Hg (MMRM)

-0.5 0 0.5 1 1.5

6 mo (N=9660) 12 mo (N=5109) 18 mo (N=2561) 24 mo (N=1076) >24 mo (N=682)

- Sitting Systolic BP
- Sitting Diastolic BP
OA/CLBP General Safety Conclusions

♦ OA/CLBP safety profile consistent with safety profile of currently approved indications

♦ Safety profile well characterized and appropriately described in the duloxetine label
Hepatic Safety Profile

Arie Regev, MD
Eli Lilly and Company
Overall Hepatic Conclusions

- Duloxetine can cause aminotransferase increases
- While there have been reports of liver injury, sometimes fatal, the evidence does not support that duloxetine causes severe drug induced liver injury, defined as liver failure leading to liver transplant or death
- Duloxetine hepatic profile well-characterized in US label
Presentation of Hepatic Results

♦ Current data in U.S. Label
♦ Clinical Trial Data
♦ Post-Marketing Data - Spontaneous reports from Lilly Safety System (LSS) and Adverse Event Reporting System (AERS)
♦ Population-Based Retrospective Cohort Study
5.2 Hepatotoxicity

There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (85/7,632) of Cymbalta-treated patients compared to 0.2% (13/5,578) of placebo-treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.
Hepatic Safety in Duloxetine Label: Placebo-controlled Studies

5.2 Hepatotoxicity

There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (85/7,632) of Cymbalta-treated patients compared to 0.2% (13/5,578) of placebo-treated patients.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.
5.2 Hepatotoxicity

There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (82/27,229) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, elevation of ALT >3 times the upper limit of normal occurred in 1.1% (85/7,632) of Cymbalta-treated patients compared to 0.2% (13/5,578) of placebo-treated patients. In placebo-controlled studies using a fixed dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease (5.2).
Clinical Trial Data:
All Duloxetine Studies
# Outcome of ALT Elevations

**All Duloxetine Studies**

<table>
<thead>
<tr>
<th>ALT Category</th>
<th>Patient Outcomes</th>
<th>Additional Follow-up Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3X and ≤5X ULN</td>
<td>N=136, n</td>
<td></td>
</tr>
<tr>
<td>Back to normal</td>
<td>89</td>
<td>9 pts: no further information</td>
</tr>
<tr>
<td>Decreasing</td>
<td>34</td>
<td>1 pt: occurred after 2 yrs DLX treatment</td>
</tr>
<tr>
<td>No additional ALT value</td>
<td>13</td>
<td>1 pt: occurred before DLX treatment</td>
</tr>
<tr>
<td>&gt; 5X and ≤10 ULN</td>
<td>N=76, n</td>
<td></td>
</tr>
<tr>
<td>Back to normal</td>
<td>49</td>
<td>96.1%</td>
</tr>
<tr>
<td>Decreasing</td>
<td>24</td>
<td>2 pts had other causes:</td>
</tr>
<tr>
<td>No additional ALT value</td>
<td>3</td>
<td>liver &amp; bone metastases (1)</td>
</tr>
<tr>
<td>&gt; 10 X ULN</td>
<td>N=38, n</td>
<td></td>
</tr>
<tr>
<td>Back to normal</td>
<td>16</td>
<td>myocardial infarction(1)</td>
</tr>
<tr>
<td>Decreasing</td>
<td>21</td>
<td>1 pt: Elevation occurred 1 month after</td>
</tr>
<tr>
<td>No additional ALT value</td>
<td>1</td>
<td>discontinuing DLX</td>
</tr>
<tr>
<td>Follow-up call: pt reported “feeling fine”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 pts had other causes:
- liver & bone metastases
- myocardial infarction

1 pt: occurred before DLX treatment
1 pt: continued on DLX, no hepatic AEs
1 pt: occurred 1 month after discontinuing DLX

96.1%

97.4%
No Hy’s Rule Cases in Duloxetine Clinical Trial Database

- No Hy’s* Rule cases
  - ALT/AST ≥ 3X ULN
  - Total bilirubin ≥ 2X ULN
  - No cholestasis, alkaline phosphatase < 2X ULN
  - No other causes

*as defined by FDA Guidance 2009
Hepatic Cases in All Duloxetine Studies: ALT ≥3X ULN and TBILI ≥2X ULN

- 3 duloxetine-treated and 2 placebo-treated patients developed increases in ALT (≥3 times ULN) and bilirubin (≥ 2 times ULN)

- Duloxetine-treated patients
  - Patient 1: Liver injury following binge drinking. Liver biopsy consistent with alcoholic cirrhosis, with granulomatous changes
  - Patient 2: Liver injury following binge drinking. Improved on duloxetine.
  - Patient 3: Cholestasis, multiple gallstones
Clinical Trial Patients Presented by Dr. Stone as “Hy’s Rule Cases”

♦ Patient 1
  • Total bilirubin elevation 1.5X ULN (< 2X ULN)
  • Patient had multiple gallstones
  • Recurrence of hepatic abnormalities 5 months post duloxetine discontinuation
  • Resolved after removal of gallstones from common bile duct

♦ Patient 2
  • Total bilirubin elevation 1.5X ULN (< 2X ULN)
  • Patient had positive test for hepatitis C virus
Predictive Value of ALT Elevations

- Elevated ALT values alone not predictive of severe hepatotoxicity (FDA guidance, July 2009)
- Monitoring of ALT values ineffective in predicting drug-induced liver injury
- Hy’s Rule cases predict severe hepatotoxicity
  - No cases with duloxetine observed in more than 29,000 patients in clinical studies
ALT Elevations in OA/CLBP vs Other Placebo-Controlled Studies

ALT Elevations at Anytime in Patients with Normal Baseline Value

<table>
<thead>
<tr>
<th></th>
<th>OA/CLBP</th>
<th>Other PBO-Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3X ULN</td>
<td>0.72%</td>
<td>1.11%</td>
</tr>
<tr>
<td>&gt;5X ULN</td>
<td>0.36%</td>
<td>0.59%</td>
</tr>
<tr>
<td>&gt;10X ULN</td>
<td>0.36%</td>
<td>0.19%</td>
</tr>
</tbody>
</table>

- No cases of Hy’s Rule in CLBP/OA clinical trials
# Clinical Significance Categories of Hepatic Events in Spontaneous Reports

## 5 Categories

1. No hepatic injury
2. Non-severe hepatic injury
3. Other significant hepatic injury (formerly called “Severe hepatic Injury”)
4. Hepatic failure
5. Fatal

### Clinically Significant - Adjudicated

| 3. Other significant hepatic injury (formerly called “Severe hepatic Injury”) | AST/ALT >10X ULN OR increase in both ALT/AST and total bilirubin levels |
| 4. Hepatic failure | As reported, not clinically supported in many cases |
| 5. Fatal | Of any cause, may not have been due to liver failure |
**Etiologic Categories of Hepatic Events in Spontaneous Reports**

- Clinically significant hepatic cases reviewed and classified independently by 2 Lilly physicians, a Lilly hepatologist and 3 external experts

<table>
<thead>
<tr>
<th>Etiologic Category</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unlikely</td>
<td>Clear compelling cause present or negative rechallenge</td>
</tr>
<tr>
<td>Possible</td>
<td>Other compelling, confounding, or contributing factors present</td>
</tr>
<tr>
<td>Probable</td>
<td>No compelling confounding or contributing factors present</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Insufficient information available</td>
</tr>
</tbody>
</table>
### Clinically Significant Hepatic Cases in Spontaneous Reports

#### Summary of Clinically Significant Hepatic Cases from Spontaneous Reports (through 2 May 2010)

<table>
<thead>
<tr>
<th></th>
<th>Indeterminate</th>
<th>Unlikely</th>
<th>Possible</th>
<th>Probable</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Significant Hepatic Injury</td>
<td>24</td>
<td>33</td>
<td>60</td>
<td>14</td>
<td>131</td>
</tr>
<tr>
<td>Hepatic Failure</td>
<td>13</td>
<td>21</td>
<td>11</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>Fatality</td>
<td>10</td>
<td>22</td>
<td>5</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>47</strong></td>
<td><strong>76</strong></td>
<td><strong>76</strong></td>
<td><strong>14</strong></td>
<td><strong>213</strong></td>
</tr>
</tbody>
</table>

Data must be interpreted within the context of the known limitations of spontaneous (voluntary) reports

- Overall number of exposures: 29.9 million
- No “probably-related” fatalities or hepatic failure
Liver Injury: Case 2 of FDA Briefing Document

2. An............................ who had been taking duloxetine for a year (long for onset) as well as furosemide and ergocalciferol presented with encephalopathy, jaundice and markedly elevated transaminases without evidence of obstruction. Hepatitis A, B and C serologies and blood cultures were negative. No pathological examination was available. The attending physician concluded the patient’s death was due acute liver failure from duloxetine.

- Duloxetine for one year
- Nausea, fatigue, changes in mental status
- Elevated cardiac enzymes (CPK-1,054, CPK-MB-18.4%), Ejection fraction-26%
- Cardiovascular evaluation: severe cardiomyopathy
- Gastroenterologist’s differential diagnosis: Ischemic hepatitis vs drug induced vs Budd Chiari
- **Lilly’s Assessment:** Ischemic liver injury due to heart failure
- **External Independent Assessment:** Agree with Lilly’s assessment
AERS Signal Detection Analysis for Duloxetine, Paroxetine, and Nefazodone

- AERS: FDA database for spontaneous reports of all drugs
- Analysis to compare duloxetine with paroxetine (no hepatic effect) and nefazodone (hepatotoxic)
- Relative reporting ratio of 1 indicates reporting of adverse event is similar to reporting of the event for all other drugs combined
- Commonly used threshold for identifying a safety signal: lower 5% confidence limit of relative reporting ratio is >2
AERS Signal Detection Analysis of Hepatic Failure for Duloxetine, Paroxetine, & Nefazodone

Hepatic failure*

Values are based on cumulative results since Q1 1995
* Medical Dictionary for Regulatory Activities (MedDRA) preferred term
Identify incidence and relative risk of liver-related events among patients who received duloxetine for depression (n=21,457) vs. venlafaxine, SSRIs, TCA, nefazodone

Each cohort was propensity score matched to duloxetine on the basis of 1-year baseline data

No statistically significant differences between duloxetine and any other antidepressant with regard to acute liver failure and liver-related death (however numbers were small)

No statistically significantly increased risk of all hepatic events combined between duloxetine and other antidepressants except for venlafaxine
Summary of Hepatic Safety Data

♦ Clinical Trial Data
  • ALT elevations transient and self-limiting
  • No Hy’s Rule cases
  • Hepatic safety profile in OA/CLBP studies similar to other indications

♦ Spontaneous Reports
  • Reports of hepatic failure, sometimes fatal, with duloxetine
    – no reported cases were unconfounded
  • Clinically significant hepatic events are very rarely reported and majority are not clearly related to duloxetine
  • AERS data suggest relative reporting of hepatic failure for duloxetine is similar to all other drugs combined and lower than that for nefazodone
Overall Hepatic Conclusions

- Duloxetine can cause aminotransferase increases
- While there have been reports of liver injury, sometimes fatal, the evidence does not support that duloxetine causes severe drug induced liver injury, defined as liver failure leading to liver transplant or death
- Chronic pain patients do not appear to be at an increased risk for hepatic events
- Current labeling adequately describes the hepatic safety profile
Risk Management Plan

Steve Knowles, MD
Eli Lilly and Company
Risk Management Plan (RMP)

♦ Detailed, regular monitoring of AE data from multiple sources

♦ Specific monitoring and assessment activities for important areas of safety profile, including
  • Hepatic injury
  • Cardiovascular outcomes
  • Suicidality
  • GI bleeding
  • Stevens-Johnson Syndrome

♦ Medication Guide addressing suicidality
Specialized Risk Assessment

Completed and Planned Pharmacoepidemiology Studies

- Hepatic
- CV
- Suicidality
- Pregnancy
- GI Bleeding
- All Risks
- Utilization

Legend:
- Planned
- Ongoing
- Complete
## Population-Based Patient Characteristics in i3 Pharmacoepidemiology Study

### Baseline Patient Characteristics by Treatment Cohort

#### Hepatic/CV Study

<table>
<thead>
<tr>
<th></th>
<th>DLX N=21,457</th>
<th>VEN N=27,443</th>
<th>SSRIs N=137,477</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidities (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>40.3</td>
<td>27.7</td>
<td>19.4</td>
</tr>
<tr>
<td>Abuse/addiction (incl. alcohol)</td>
<td>15.8</td>
<td>14.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Pain-related condition (incl. FM, DPNP, LBP)</td>
<td>36.2</td>
<td>17.2</td>
<td>13.7</td>
</tr>
<tr>
<td>Hepatic</td>
<td>9.8</td>
<td>8.6</td>
<td>7.0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>47.3</td>
<td>35.8</td>
<td>35.7</td>
</tr>
</tbody>
</table>
Incidence Rate Ratio of All Hepatic Events Combined: i3 Pharmacoepidemiology Study

<table>
<thead>
<tr>
<th>Drug</th>
<th>IRR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Comparison to Duloxetine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>1.08</td>
<td>(0.46 - 2.57)</td>
</tr>
<tr>
<td>Venlafaxine*</td>
<td>0.34</td>
<td>(0.12 - 0.95)</td>
</tr>
<tr>
<td>TCA</td>
<td>0.56</td>
<td>(0.18 - 1.71)</td>
</tr>
<tr>
<td>Untreated</td>
<td>0.64</td>
<td>(0.15 - 2.67)</td>
</tr>
<tr>
<td>Non-depressed</td>
<td>0.30</td>
<td>(0.10 – 0.93)</td>
</tr>
</tbody>
</table>

*no significant difference in severe outcomes (liver failure: duloxetine n=2, venlafaxine n=1; death: duloxetine n=1, venlafaxine n=1)
### Incidence Rate Ratio of Cardiovascular Events: i3 Pharmacoepidemiology Study

<table>
<thead>
<tr>
<th>Drug</th>
<th>IRR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Comparison to Duloxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>1.01</td>
<td>(0.66 - 1.55)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1.01</td>
<td>(0.68 - 1.49)</td>
</tr>
<tr>
<td>TCA</td>
<td>1.01</td>
<td>(0.58 - 1.75)</td>
</tr>
<tr>
<td>Untreated</td>
<td>0.79</td>
<td>(0.41 - 1.50)</td>
</tr>
<tr>
<td>Non-depressed</td>
<td>0.51</td>
<td>(0.32 - 0.81)</td>
</tr>
</tbody>
</table>
Propensity Matched Suicide Attempts in Newly Diagnosed Antidepressant Users: Pharmetrics Study

- Comorbid pain ~ 1/3 of patients
- Suicide attempt risk: no significant difference between duloxetine and other antidepressants
- Suicide attempt rates were highest in month before diagnosis
Estimating On-label Use

- ICD-9 codes are a proxy to track use and diagnoses related to medications
- Widely recognized practicality: ICD-9 selection driven by reimbursement considerations
- Superbill: allows the capture and communication of codes most commonly used in office-based, outpatient practice to payers
  - Can limit the ability to accurately identify a specific diagnosis
    - For example, the Family Practice Management superbill only includes a single ICD-9 code for depression: 311 (Depressive Disorder NOS)
- HEDIS position also supports use of 311 for MDD
  - Published codes to identify MDD include: 296.20-296.25, 296.30-296.35, 298.0, 300.4, 309.1, 311
- When estimating on-label use, the inclusion of relevant ICD-9 codes should reflect common practice patterns. To do otherwise may inaccurately portray on-label utilization.
Risk Minimization

♦ USPI is the primary risk minimization tool

♦ Medication Guide
  • Proposed updated comprehensive Medication Guide covering all major risks from USPI

♦ Assess the appropriateness and effectiveness of risk minimization activities in consultation with FDA
Overall Benefit Risk Assessment for Duloxetine in Chronic Pain

Daniel J. Clauw M.D.
Professor of Anesthesiology, Medicine (Rheumatology) and Psychiatry
Director, Chronic Pain and Fatigue Research Center
The University of Michigan
Overview

- Chronic pain states often “mixed” pain states
  - Subset of individuals displaying augmented CNS pain processing (diffuse hyperalgesia)
- Modifications of current treatment paradigms needed
  - Inclusion of CNS contribution to pain
- Duloxetine
  - Different MOA
  - Centrally-acting analgesic
  - New option to clinical practice
Potential Framework\textsuperscript{1}: Benefit-Risk

- Severity of disease state
- Unmet medical needs
- Clinical benefit of duloxetine treatment
- Risks with duloxetine and current treatments
- Risk management

\textsuperscript{1} Based on: http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM210155.pdf
Benefit-Risk Assessment

- Science provides data to inform our analyses of benefit risk, it does not provide the answers – judgment is required
- Regulators must make judgments on benefit risk at the population level
- Doctors and patients must translate the population benefit-risk information to make judgments on an individual patient level
Rationale for New Class of Analgesics for Chronic Pain

• Efficacy benefits and limitations of current therapies
  • NSAIDs, acetaminophen, and opioids: Effect sizes of 0.2 - 0.4 \(^ {1,2}\)
  • Surgical therapies
    • Arthroplasty does not predictably relieve pain of OA \(^ {3}\)
    • Laminectomy often does not relieve pain in CLBP, especially in long term studies
• Safety and tolerability of current therapies
  • Current options being reduced by more recently recognized safety issues of commonly used analgesics
    • Acetaminophen
      • Acetaminophen overdose is the leading cause of acute liver failure in US \(^ {4}\)
    • NSAIDs - GI Bleeds, cardiovascular side effects, fatalities \(^ {1}\)
    • Opioids - Illicit use, fatalities \(^ {5}\)

Current Treatment Algorithm for OA Pain

- Surgery
- Opioids
- Prescription NSAIDs
- Over-the-counter NSAIDs
- Acetaminophen
- Patient education
  - Weight reduction
  - Exercise, physical therapy, assistive devices

Cochrane and other Meta-analyses
Analgesic Efficacy for OA of Knee and Hip

- **Acetaminophen**
  - Pain decreased *4 mm* more than placebo on 1-100 scale\(^1\)
  - Low effect size

- **Oral NSAIDs**
  - Greater pain relief than acetaminophen in comparator trials\(^1\)
  - Low to modest overall effect size
    - \(SMD \, -0.32\) in pooled meta-analyses of all trials, but \(\, -0.23\) in trials that did not exclude NSAID non-responders\(^2\)

---

Cochrane Reviews 2006 & 2009: Analgesic Efficacy for OA of Knee and Hip

- **Tramadol with or without acetaminophen**
  - Average pain improvement: 8.5 mm better than placebo on 0-100 scale\(^1\)

- **Opioids**
  - Average pain improvement: SMD -.36\(^2\)
  - “The small to moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events. Nontramadol opioids should therefore not be routinely used, even if osteoarthritic pain is severe”

---

Meta-analyses of NSAIDs and Opioids in Chronic Low Back Pain

• NSAIDS
  • “Statistically significant effects were found in favor of NSAIDs compared with placebo, but at the cost of statistically significant more side effects. There is moderate evidence that NSAIDs are not more effective than paracetamol for acute low back pain, but paracetamol had fewer side effects”

• Opioids
  • “Analysis of active treatment compared with placebo revealed a composite mean standardized difference .19 (p=.136) which reflects a nonsignificant reduction in pain in patients receiving opioid treatment compared to those receiving nonopioids or placebo”
  • “The prevalence of lifetime substance use disorders is as high as 56%”

Duloxetine in Chronic Pain
Consistency of Effect

Effect Size on BPI Average Pain
Average Pain Mean Change to Endpoint (LOCF)
“During the past decade, the use of opioid analgesic drug products to treat non-cancer, chronic pain has increased exponentially in response to this new paradigm”

“Over this same time period, however, there has been an increasing problem with the inappropriate prescribing, misuse, and abuse of prescription opioid drug products in the United States that has resulted in a significant public health crisis of addiction, overdose, and death.”

SCOPE Working Group data were also presented suggesting problems were not confined to long-acting opioids
Serious Adverse Events of NSAIDS

• Cardiovascular\textsuperscript{1,2}
  • Estimated excess rates of death from all NSAIDs may be approximately 1:10,000

• Gastrointestinal\textsuperscript{2,3}
  • As high as 1 – 4\% of individuals will experience a symptomatic GI bleed
  • Excess death from GI bleed for all NSAIDs have been reported to be between 1:2000 and 1:10,000 individuals taking NSAIDs for a year

Safety and Tolerability of Duloxetine in CLBP and OA

• The risk profile of duloxetine is well known and described (hepatic, suicidality, bleeding)

• No new safety signals have appeared in the clinical trials of duloxetine in patients with osteoarthritis and chronic low back pain

• No signal suggesting synergistic toxicity with other analgesics
  • NSAIDs and bleeding
  • Acetaminophen and hepatotoxicity

• Extensive use in clinical practice in patients with MDD and DPNP offers safety information about a broad population with significant co-morbidities and concomitant medications.
Current Treatment Algorithm for OA Pain

Surgery
Opioids
Prescription NSAIDs
Over-the-counter NSAIDs
Acetaminophen
Patient education
Weight reduction
Exercise, physical therapy, assistive devices

Conclusion

• Duloxetine mechanism of action is different from that of opioids and NSAIDs

• The efficacy of duloxetine in patients with OA and CLBP is comparable to that of existing treatments

• No new safety and tolerability risks have been identified for OA and CLBP
  • Broad population has already been exposed to drug

• Toxicity is different than NSAIDs and opioids, but in many patients with chronic pain the benefit risk profile may favor duloxetine over one or both of those classes
Conclusion

- Large number of patients still suffer from chronic pain
- Duloxetine offers benefit:
  - New treatment option with a different mechanism of action
  - In multiple pain states (DPNP, FM, OA, CLBP)
  - Analgesic effect size comparable to that of NSAIDs and opioids
- Safety profile of analgesics, including duloxetine differ
- Risk of duloxetine:
  - Duloxetine well-established in patients with MDD, GAD, DPNP, FM (29.9 million exposures as of May 2010)
  - No new risks identified in the OA and CLBP populations
- The benefit/risk balance for duloxetine remains favorable in the chronic pain population
♦ Back Up Slides Shown 8-19-10
OA Studies
SF-36 Quality of Life (LOCF)

Study OA-FG

Study OA-EP

*p<.05 vs PBO

5277.01
CLBP Studies
SF-36 Quality of Life (LOCF)

Study CLBP-EN

Study CLBP-GC

* p<.05 vs PBO

5278.01
Study CLBP-EO
SF-36 Quality of Life (LOCF)

*p<.05 vs PBO

*p<.05 vs PBO
CLBP Studies: BPI-Interference on General Function (LOCF)

* \( p < .05 \) vs PBO
CLBP Studies: 30% and 50% Response Rates (BOCF)
Effect of Duloxetine Dose on Bleeding Events in All Fixed-Dose Placebo-Controlled Studies

Incidence of All Treatment Emergent Bleeding

Percent of Patients

DLX 60 (N=913)

1.97%

0.22%

DLX 120 (N=904)

1.66%

0.44%
ALT Elevations by Dose in Fixed-Dose Placebo-Controlled Studies

<table>
<thead>
<tr>
<th>ALT Elevation</th>
<th>DLX 60 mg/day N=749, n (%)</th>
<th>DLX 120 mg/day N=743, n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3X ULN</td>
<td>5 (0.7)</td>
<td>12 (1.6)</td>
<td>.089</td>
</tr>
<tr>
<td>&gt; 5X ULN</td>
<td>3 (0.4)</td>
<td>6 (0.8)</td>
<td>.325</td>
</tr>
<tr>
<td>&gt; 10X ULN</td>
<td>2 (0.3)</td>
<td>1 (0.1)</td>
<td>.558</td>
</tr>
</tbody>
</table>

- Higher duloxetine dose associated with numerical increase in mild ALT elevations, but not statistically significant
- OA and CLPB – no apparent dose relationship observed in elevations of ALT

Fixed Dose Studies: 3 DPNP studies, 2 FM studies, 1 CLBP, 1 GAD, 1 MDD from Overall Duloxetine Exposures Analyses Set
Effect of Dose on Spontaneously Reported Cases of Hepatic Events (Through 2007)

Overall DLX Prescriptions (N>4.2 M) by DLX Dose Categories

- **LOW**: 0 - 45.9 mg
- **MED**: 46 - 79.9 mg
- **HIGH**: 80 - 180 mg

Incidence of Clinically Significant US Cases (N=78) by DLX Dose Categories

- **LOW**: 0 - 45.9 mg
- **MED**: 46 - 79.9 mg
- **HIGH**: 80 - 180 mg

Prescription totals through September 2007
Data must be interpreted within the context of the known limitations of spontaneous (voluntary) reports.
**Duloxetine 120 mg: Efficacy in CLBP/OA Dose Escalation Studies: (BOCF)**

Subset of DLX 60 mg Patients Increased to 120 mg at Week 7

<table>
<thead>
<tr>
<th>Study</th>
<th>Non-Responders N</th>
<th>Outcomes Wk 7 DLX 60 mg</th>
<th>Outcomes at Week 13 DLX 120 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Responders n (%)</td>
<td>D/C (Wk 7-13) n (%)</td>
</tr>
<tr>
<td>CLBP-EN</td>
<td>27</td>
<td>6 (22%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>OA-FG</td>
<td>33</td>
<td>12 (36%)</td>
<td>6 (18%)</td>
</tr>
</tbody>
</table>
### Duloxetine 120 mg: Efficacy in OA Dose Re-Randomization Study (BOCF)

OA-EP: Subset of DLX Patients (Wk 1-6) and DLX Non-Responders (Wk 7-13)

<table>
<thead>
<tr>
<th>DLX Dose Group (mg)</th>
<th>Outcomes at Week 7 DLX 60 mg</th>
<th>Outcome at Week 13 DLX 60 and 120 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Responders, n</td>
<td>Responders n (%)</td>
</tr>
<tr>
<td>60/60</td>
<td>14</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>60/120</td>
<td>14</td>
<td>5 (36%)</td>
</tr>
</tbody>
</table>

5901.01
Duloxetine 120 mg

- Previously approved dose for DPNP
- Currently approved dose for MDD and GAD
- Efficacy of duloxetine 120 mg compared to 60 mg dose
  - numeric advantage in all fixed dose DPNP and FM studies
  - numeric advantage in OA dose re-randomization study (OA-EP)

![Chart showing change in average pain severity after DLX dose re-randomization in OA-EP (Wk 7-13)]
## Duloxetine in OA Studies

### WOMAC Subscale (BOCF)

<table>
<thead>
<tr>
<th>WOMAC Subscale</th>
<th>OA-FG</th>
<th>OA-EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>p=.515</td>
<td>p=.065</td>
</tr>
<tr>
<td>Stiffness</td>
<td>p=.122</td>
<td>p=.023</td>
</tr>
<tr>
<td>Physical Function</td>
<td>p=.149</td>
<td>p=.028</td>
</tr>
<tr>
<td>Total</td>
<td>p=.239</td>
<td>p=.038</td>
</tr>
</tbody>
</table>

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
30% Response Rate of Duloxetine Across Chronic Pain States at 3-Months (BOCF)

*p < .05 vs PBO
50% Response Rate of Duloxetine Across Chronic Pain States at 3-Months (BOCF)

* p<.05 vs PBO
# Baseline and Disease Characteristics

## CLBP and OA Studies

<table>
<thead>
<tr>
<th>Variables</th>
<th>CLBP-GC N=401</th>
<th>CLBP-EN N = 236</th>
<th>CLBP-EO N = 404</th>
<th>OA-FG N = 256</th>
<th>OA-EP N = 231</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Split &gt;55 yrs in CLBP and &gt;65 years in OA(%)</td>
<td>52</td>
<td>40</td>
<td>52</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79</td>
<td>76</td>
<td>82</td>
<td>81</td>
<td>86</td>
</tr>
<tr>
<td>Ongoing NSAID Use, Yes (%)</td>
<td>--</td>
<td>31</td>
<td>41</td>
<td>39</td>
<td>51</td>
</tr>
<tr>
<td>WOMAC Physical Function (mean)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>WOMAC Total (mean)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td>RMDQ-24 (mean)</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Duration of Pain (mean yrs)</td>
<td>8.5</td>
<td>9.2</td>
<td>11.7</td>
<td>7.4</td>
<td>9.2</td>
</tr>
<tr>
<td>Quebec Task Force Class II (%)</td>
<td>13</td>
<td>34</td>
<td>22</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
### Duloxetine in OA and CLBP Studies
#### Racial Demographics

<table>
<thead>
<tr>
<th>Race</th>
<th>OA-FG (N=256), %</th>
<th>OA-EP (N=231), %</th>
<th>CLBP-EN (N=236), %</th>
<th>CLBP-GC (N=401), %</th>
<th>CLBP-EO (N=404), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>1.2</td>
<td>5.2</td>
<td>5.1</td>
<td>2.5</td>
<td>8.2</td>
</tr>
<tr>
<td>Caucasian</td>
<td>97.7</td>
<td>84.0</td>
<td>74.6</td>
<td>95.3</td>
<td>79.7</td>
</tr>
<tr>
<td>East Asian</td>
<td>0.4</td>
<td>1.3</td>
<td>0.9</td>
<td>--</td>
<td>0.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.8</td>
<td>8.2</td>
<td>18.6</td>
<td>2.0</td>
<td>10.2</td>
</tr>
<tr>
<td>Native American</td>
<td>--</td>
<td>1.3</td>
<td>0.9</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>West Asian</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Episodic use of short-acting analgesics including narcotics (eg. APAP, codeine)
• Allowed for breakthrough index pain or unrelated acute pain
• Max Use: No more than 3 consecutive days and 20 cumulative days

<table>
<thead>
<tr>
<th>Episodic Use Analgesic</th>
<th>DLX60, N=198 %</th>
<th>PBO, N=203 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 Rescue Analgesic</td>
<td>36.4</td>
<td>47.3</td>
</tr>
<tr>
<td>Other</td>
<td>19.2</td>
<td>21.7</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>12.6</td>
<td>20.7</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>5.1</td>
<td>9.4</td>
</tr>
<tr>
<td>Naproxen</td>
<td>3.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Codeine</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Metamizole sodium</td>
<td>0.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Indometacin</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Dexketoprofen</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>0.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Duloxetine CLBP Studies: Cumulative Improvement in Pain from Baseline (BOCF)

Cumulative % of Improvement in Average Pain Score

- **CLBP-GC**: p<.05 vs PBO
- **CLBP-EN**: p=.255

- **DLX 60 (N=198)**
- **PBO (N=203)**

- **DLX 60/120 (N=109)**
- **PBO (N=115)**
### Duloxetine NNT for 30% Response: All Placebo-Controlled Pain Studies (LOCF)

#### All Placebo-Controlled Pain Studies

<table>
<thead>
<tr>
<th>Studies and DLX Doses</th>
<th>NNT Range (LOCF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPNP: 3 Studies</td>
<td>3.6 - 5.7</td>
</tr>
<tr>
<td>- 60 and 120 mg DLX</td>
<td></td>
</tr>
<tr>
<td>FM: 2 Studies</td>
<td>4.5, 6.8</td>
</tr>
<tr>
<td>- 60 and 120 mg DLX</td>
<td></td>
</tr>
<tr>
<td>OA: 2 Studies</td>
<td>4.7, 6.8</td>
</tr>
<tr>
<td>- 60 and 120 mg DLX</td>
<td></td>
</tr>
<tr>
<td>CLBP: 2 Studies</td>
<td>7.6, 12.2</td>
</tr>
<tr>
<td>- 60 and 120 mg DLX</td>
<td></td>
</tr>
</tbody>
</table>
## Number Needed to Treat (NNT): 30% Response in OA and CLBP (BOCF)

### Approved Drugs Only

NNT- for 30% Response Criteria

<table>
<thead>
<tr>
<th></th>
<th>Naproxen 1000 mg</th>
<th>Ibuprofen 2400 mg</th>
<th>Celecoxib 200 mg</th>
<th>Etoricoxib(^3) 30 – 90 mg</th>
<th>Duloxetine 60-120 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OA</strong></td>
<td>4.8</td>
<td>12.0</td>
<td>4.7</td>
<td>30 mg: 4.3</td>
<td>6.9, 11.6</td>
</tr>
<tr>
<td><strong>CLBP</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>60 mg: 7.5</td>
<td>7.8, 14.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90 mg: 6.9</td>
<td></td>
</tr>
</tbody>
</table>

Placebo-controlled studies of 12-13 weeks duration

Fig 3.8: Subgroup Analysis of LS Mean Change in BPI Average Pain by NSAID Use in the OA and CLBP Studies

Combined OA-FG and OA-EP

Combined CLBP-EN and CLBP-EO

Abbreviations:  BPI = Brief Pain Inventory; CLBP = chronic low-back pain; DLX = duloxetine; LSMean = least-squares mean; N = number of patients in the treatment arm; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PBO = placebo.
Fig. 6.1: Analgesic Effect of Pharmacological Treatments for Low Back Pain