Objectives

1. Define chronic pain
2. Identify conditions associated with non-oncologic chronic pain
3. Discuss patient evaluation
4. Review fibromyalgia syndrome (FMS)
5. Discuss pharmacologic treatment options for FMS
6. Review clinical trial data for milnacipran (Savella®) and comparison of trial data for amitriptyline (Elavil®), duloxetine (Cymbalta®), and milnacipran (Salvella®)
1. Definition of Chronic Pain (1)
   a) Pain not directly related to neoplastic involvement, associated with a chronic medical condition or extending in duration beyond the expected temporal boundary of tissue injury and normal healing, and adversely affecting the function or well-being of the individual.
2. Conditions associated with Chronic Pain (1)
   a) Diabetes, multiple sclerosis, post-traumatic injury, FMS
3. Specific pain conditions
   a) Complex regional pain syndrome (CRPS) (1)
   b) Neuropathic pain (1)
      i) Fewer than 60% of individuals receive or experience partial relief from neuropathic pain using approved medications (NNT ranges from 2 to 6) (2)
4. Patient Evaluation (1) (3)
   a) History and physical exam
      i) Pain history: general medical history with emphasis on the chronological and symptomatology of presenting complaints
      ii) History of Present Illness (HPI): onset, quality, intensity, distribution, duration, course, and sensory and affective components of the pain, exacerbating and relieving factors
      iii) Previous tests, treatments, and current therapies
         1. Medication adverse effects should be ruled out as a cause of symptoms
      iv) Orthopedic and neurological examination
   b) Diagnostic procedures
      i) Blood tests to rule out disease causes of patient symptoms
         1. systemic inflammatory disorder, renal and hepatic failure, hypothyroidism, myositis, and other diseases
   c) On-going follow-up evaluations
5. FMS – General Information
   a) Etiology (3) (4)
      i) Cause unknown
      ii) There appears to be a genetic component as FMS often runs in families
         1. Frequency of FMS among first degree relatives is 6.4%
      iii) Certain events seem to precipitate onset
         1. Stressful and traumatic events like car accidents, post traumatic stress disorder (PTSD), repetitive injuries, illness, other diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and chronic fatigue syndrome
   b) Characteristics (3) (4)
i) Widespread pain, abnormal pain processing, sleep disturbance, fatigue, and depression
ii) Adults with FMS are 3.8 times more likely to have major depression
iii) Chronic pain and other somatic symptoms, but without apparent tissue damage or inflammation
iv) Heterogeneous condition
c) Other possible symptoms & concurrent conditions (3)
i) Rheumatic conditions (RA, SLE, AS) up to 25-65%
ii) morning stiffness
iii) Tingling or numbness in the hands and feet
iv) Headaches including migraines
v) Irritable bowel syndrome
vi) “Fibro fog” problems with thinking or memory
vii) Painful menstrual periods
viii) Other pain syndromes
   1. People with FMS are often react strongly to stimuli that other people would not find painful such as light touch
d) Epidemiology
i) Prevalence (3) (4)
   1. 2005: 2%, ~5 million adults (3.4% female vs 0.5% male)
   2. FMS primarily affects adult women but it also can occur in males and children
   3. Diagnosis usually occurs doing middle age
   4. Prevalence increases with age.
ii) Mortality (3)
   1. 23 deaths per year from 1979 to 1998
   2. 1998 “myositis and myalgia, unspecified” 0.45% of all deaths attributed to arthritis and other rheumatic conditions.
iii) Morbidity (3)
   1. ~7,440 hospitalizations for FMS occurred in 1997
   2. 1.8 million physician office visits per year
   3. 187,000 outpatient department visits per year
   4. 266,000 emergency department visits per year
   5. Patients with FMS experience and average of 1 hospitalization every 3 years
e) Cost (3)
   i) Average yearly service utilization costs/person = $2,274
   ii) Total annual costs (direct and indirect)/person = $5,945
6. FMS - Diagnosis
   a) In 1990 the American College of Rheumatology (ACR) created the first official diagnostic criteria for FMS. (4) (5) (table 1)
i) The 1990 ACR criteria remained the “gold standard” for FMS diagnosis until ACR published updated guidelines in 2010. (5) (3)

1. History of widespread
2. Pain in 11 of 18 tender point sites on digital palpation (figure 1)

Table 1: The ACR 1990 criteria for the classification of FMS from Wolfe et al (4)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of widespread pain</td>
<td>Pain is considered widespread when all the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. “Low back” pain is considered lower segment pain.</td>
</tr>
</tbody>
</table>
| Pain in 11 of 18 tender sites on digital palpation | Pain, on digital palpation, must be present in at least 11 of the following 18 tender point sites:  
  - Occiput: bilateral, at the suboccipital muscle insertions  
  - Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7  
  - Trapezius: bilateral, at the midpoint of the upper border  
  - Supraspinatus: bilateral, at origins, above the scapula spine near the medial border  
  - Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces  
  - Lateral epicondyle: bilateral, 2 cm distal to the epicondyles  
  - Gluteal: bilateral, in upper outer quadrants in anterior fold of muscle  
  - Greater trochanter: bilateral, posterior to the trochanteric prominence  
  - Knee: bilateral, at the medial fat pad proximal to the joint line  

Digital palpation should be performed with an approximate force of 4 kg

For a tender point to be considered “positive” the subject must state that the palpation was painful. “Tender” is not to be considered “painful”

*For classification purposes, patients will be said to have FMS if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of FMS.

Figure 1: Tender point locations for the 1990 classification criteria for FMS taken from Wolfe, et al. (4)
Non-Opioid Treatments for Pain: Fibromyalgia

The American College of Rheumatology Preliminary Diagnostic Criteria for FMS and Measurement of Symptom Severity (6)

**Objectives**
- Identify non-tender point diagnostic criteria for FMS to provide an alternative method of diagnosis
- Integrate severity scale-based symptoms in the new clinical criteria
  - Suitable for primary care
  - Helpful in longitudinal follow-up
- Develop a FMS symptom severity (SS) scale

**Design**
- 2-stages with the initial stage was designed to create models for, surrogate classification criteria, diagnostic criteria and a severity scale. The second phase assessed whether a shorter more practical physician questionnaire could be used to categorize FMS

**Phase One**

**Physicians**
- 30 physicians randomly selected from a list of 113 ACR members
- 10 defined as “experts” because they had published on the topic of FMS.
  - 5 selected from the authors
- Must be certain they would see 10 FMS patients and 10 non-inflammatory control patients within 4-months
- Experienced with FMS patients and FMS tender point examination

**Patient**

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>Patients completed study forms before seeing the physician</th>
<th>Clinic staff checked forms for completeness</th>
</tr>
</thead>
</table>

**Patient Variables**

<table>
<thead>
<tr>
<th>FMS Patients</th>
<th>Control Patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age ± SD (years)</td>
<td>54.6 ± 12.9</td>
<td>52.3±12.2</td>
</tr>
<tr>
<td>Males (%)</td>
<td>8.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Non-Hispanic whites (%)</td>
<td>86.8</td>
<td>85.9</td>
</tr>
<tr>
<td>Education level ± SD (years)</td>
<td>14.2 ± 2.1</td>
<td>14.3 ± 2.2</td>
</tr>
</tbody>
</table>

- FMS patients (n=258)
  - Previous diagnosis of FMS by clinical grounds or 1990 ACR diagnostic criteria by the study physician
  - Enrolled as arriving in clinic for regular care
- Previously diagnoses with FMS but found to not currently meet 1990 ACR diagnostic criteria classified as “prior fibromyalgia”
- Control patients (n=256)
  - Patients with previous diagnosis of a non-inflammatory painful disorder such as degenerative neck and back syndromes or regional disorders, osteoarthritis, tendonitis, or similar disorders diagnosed by the study physician
  - Not diagnosed previously with FMS
  - Same sex as matching FMS patient
  - No more than 10 years younger or older than matching FMS patient

**Study Variables**

- Pain in 19 body areas during the last week from the widespread pain index (WPI) previously described as part of the Regional Pain Scale
- WPI score was also analyzed using the following categories:
  - Category 0 = 0
  - Category 1 = 1-3
  - Category 2 = 4-6
  - Category 3 = ≥ 7
- Seven categorical symptom scales
- Symptom assessment utilized the following terms:
  - Pain, fatigue, trouble with sleep, trouble with anxiety or depression, problems awakening unrefreshed, and overall severity of your arthritis or FMS problem
- Categories:
  - Category 0 = No problem
Non-Opioid Treatments for Pain: Fibromyalgia

| Category 1 = Slight or mild problems, generally mild or intermittent  
| Category 2 = moderate, considerable problems, often present and/or at a moderate level  
| Category 3 = severe, pervasive, continuous, life-disturbing problems  
| Four visual analog scales (VAS)  
| Scored zero (none, no problem) to ten (severe, major problem)  
| Severity of pain over one week  
| no pain to severe pain  
| How much of a problem was fatigue or tiredness over the past week?  
| Fatigue is no problem to fatigue is a major problem  
| How much of a problem has sleep (i.e., resting at night) been over the past week?  
| Sleep is no problem to sleep is a major problem  
| How much of a problem has waking unrefreshed been over the past week?  
| Waking up unrefreshed is no problem to waking up unrefreshed is a major problem  
| Health Assessment Questionnaire II functional disability scale  
| Number of medications used in the past month to control pain  
| Extent of morning stiffness  
| Somatic symptoms  
| Review of 3 month history of 56 symptoms (see Appendix C)  

| Physician Variables  
| Certainty of the prior diagnosis from 0 = very uncertain to 10 = very certain  
| ACR tender point count (0-18)  
| Same WPI as that patient completed  
| Presence of muscle pain, irritable bowel syndrome, fatigue, cognitive problems, muscle weakness, headache, pain/cramps in the abdomen, paresthesias, dizziness, sleep problem, depression, constipation, diarrhea, interstitial cystitis, anxiety, and muscle tenderness.  
| Classified patients as having few or no somatic symptoms, a moderate number of symptoms, or a great deal of symptoms  

| Phase Two  
| Physicians  
| Recruitment followed the same process as phase one except no known fibromyalgia experts were recruited  
| Patients  
| Recruitment followed the same process as phase one  
| Patients did not fill out a questionnaire  

| Physician Variables  
| Simplified questionnaire  
| Categorical WPI  
| Question about widespread pain  
| Provided with a list of widespread pain regions  
| Tender point examination  
| Presence or absence of muscle pain, muscle tenderness, and irritable bowel syndrome  
| Rating of somatic symptoms as few or no symptoms, a moderate number if symptoms, or a great deal of symptoms  

Table 2: 2010 ACR preliminary FMS diagnostic criteria (6)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>A patient satisfies diagnostic criteria for FMS if the following 3 conditions are met:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. Widespread pain index (WPI) $\geq 7$ and symptom severity (SS) scale score $\geq 5$ or WPI 3-6 and SS scale score $\geq 9$</td>
</tr>
<tr>
<td></td>
<td>2. Symptoms have been present at a similar level for at least 3 months</td>
</tr>
<tr>
<td></td>
<td>3. The patient does not have a disorder that would otherwise explain the pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ascertainment</th>
<th>1. WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Shoulder girdle, left</td>
</tr>
<tr>
<td></td>
<td>Shoulder girdle, right</td>
</tr>
<tr>
<td></td>
<td>Upper arm, left</td>
</tr>
<tr>
<td></td>
<td>Upper arm, right</td>
</tr>
<tr>
<td></td>
<td>Lower arm, left</td>
</tr>
<tr>
<td></td>
<td>Lower arm, right</td>
</tr>
</tbody>
</table>

|          | 2. SS scale score: |
|          | Fatigue |
|          | Waking unrefreshed |
|          | Cognitive symptoms |
|          | For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale: |
|          | 0 = no problem |
|          | 1 = slight or mild problems, generally mild or intermittent |
|          | 2 = moderate, considerable problems, often present and/or at a moderate level |
|          | 3 = severe: pervasive, continuous, life-disturbing problems |
|          | Considering somatic symptoms in general, indicate whether the patient has: * |
|          | 0 = no symptoms |
|          | 1 = few symptoms |
|          | 2 = a moderate number of symptoms |
|          | 3 = a great deal of symptoms |
|          | The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12. |

*Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud’s phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.
1. Assessing Treatment (5)
   a) The Outcome Measures in Rheumatology Clinical Trials (OMERACT) FMS working group has defined three levels of symptom domains that should be assessed in clinical trials (figure 2)

   Figure 2 Domains of FMS. The diagram reflects the hierarchy of symptoms. Taken from Mease and Choy 2009. (5)

   i) Domain 1 “Core symptoms”
      1. Pain
         • Measurements: Visual Analogue Score (VAS) and multi-question assessments such as the Brief Pain Inventory (BPI)
         • Patient Global Impression of Change (PGIC)
      2. Tenderness
      3. Fatigue
         • Measurements: Multidimensional Fatigue Inventory (MFI) or Multidimensional Assessment of Fatigue Instrument
      4. Patient global sense of well-being
         • Measurements: VAS or Likert scale
      5. Multi-dimensional function including physical and social and psycho-emotional aspects of function.
         • Measurements: FMS Impact Questionnaire (FIQ) or the more general SF-36 questionnaire.
      6. Sleep disturbance
   ii) Domain 2
1. Depression
2. Dyscognition
3. Cognitive dysfunction
   • Measurements: Multiple Ability Self-Report Questionnaire (MASQ)

iii) Domain 3:
   1. Stiffness
   2. Anxiety
   3. Biomarkers like cerebrospinal fluid neuropeptide and neuroimaging

b) Outcomes evaluation in clinical trials
   i) Individual measurements of pain, global patient well-being, and global patient functioning
   ii) Composite measurements where a patient is defined as a “responder” if they achieve a predefined clinically meaningful improvement at time intervals of 3 years to 6 months.

2. Pharmacologic treatment - Overview

Table 3: Drugs with positive effects on FMS in RCTs from Sommer (3)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength of Evidence</th>
<th>Recommended Dose Range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (Elavil®)</td>
<td>1a</td>
<td>10-50 mg</td>
<td>Large body of evidence, frequent side effects</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta®)</td>
<td>1a</td>
<td>30-60 mg</td>
<td>FDA approved, long-term efficacy shown</td>
</tr>
<tr>
<td>Milnacipran (Savella®)</td>
<td>1a</td>
<td>25-200 mg</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Pregabalin (Lyrica®)</td>
<td>1a</td>
<td>150-450 mg</td>
<td>FDA approved, long-term efficacy shown</td>
</tr>
<tr>
<td>Gabapentin (Neurontin®)</td>
<td>1b</td>
<td>1200-2400 mg</td>
<td>One large RCT</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>2a</td>
<td>10-40 mg</td>
<td>An antidepressant and muscle relaxant. Not widely available outside the United States. RCTs included in this meta-analysis were short-term and of the low quality</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>2a</td>
<td>20-60 mg</td>
<td>Three small RCT</td>
</tr>
<tr>
<td>Paroxetine (Paxil®)</td>
<td>2b</td>
<td>20 mg</td>
<td>One large RCT</td>
</tr>
<tr>
<td>Tramadol (Ultram®, Ultracet®)</td>
<td>2b</td>
<td>50-300 mg</td>
<td>Two RCTs of the tramadol 150 mg/acetaminophen 1300mg</td>
</tr>
</tbody>
</table>

Oxford classification of levels of evidence: 1a: systematic review (with homogeneity) of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort study or low-quality RCT; 2b: Individual cohort study or low-quality RCT.

a) Serotonin and norepinephrine modulation in FMS
   i) Tricyclic Antidepressants (TCAs) (5)
      1. Beneficial effect on sleep quality, a more variable and moderate effect on pain and overall sense of well-being
      2. Sustainability of effect over time is suspect
      3. Tolerability problems
      4. Inhibit serotonin and norepinephrine reuptake but also bind to adrenergic receptors, histaminergic receptors, cholinergic receptors, and multiple ion channels. (7)
ii) Selective Serotonin Reuptake Inhibitors (SSRI)
   1. Do not significantly decrease pain
   2. Generally well tolerated
   3. Useful as adjuvant therapy

iii) Selective Norepinephrine Reuptake Inhibitors (SNRI)
   1. Venlafaxine (Effexor®) shows little benefit especially at lower doses
   2. Duloxetine (Cymbalta®) demonstrated efficacy in two pivotal trials
   3. Milnacipran (Savella®) approved only for FMS in the United States
      • Excluded depression patients from the United States trial
      • Milnacipran differs from other SNRIs in that it is approximately 3 times more potent for norepinephrine reuptake inhibition than serotonin reuptake inhibition (7)

b) Antiepileptic drugs (5)
   i) Pregabalin (Lyrica®) was the first FDA approved FM therapy
      1. Demonstrated improvement in pain and sleep
      2. Efficacy demonstrated for long term use

   ii) Gabapentin (Neurontin®) showed efficacy in multiple FM domains
      1. Pain, Patient Global Impression of Change rating (PGIC), function, and sleep

   c) Sedative Hypnotics
   i) Sodium oxybate (Xyrem®)
      1. A form of Gamma hydroxybutyrate (GHB)
      2. Evaluated in an 8 week phase 2 study in 88 FM patients
         • Improvement in pain, patient global improvement, function (FIQ), fatigue, and sleep quality
      3. 12 week larger trial confirmed results
      4. Highly regulated because of potential for abuse

ii) Zolpidem (Ambien®)
   1. Improved sleep but not pain

d) Analgesics
   i) Opiates
      1. Not proven to reduce FMS pain
      2. Addictive potential
      3. Theoretically can cause opioid-induced hyperalgesia.

   ii) Tramadol (Ultram®)
      1. Demonstrated efficacy in pain and several subscales of the FIQ and SF-36 function measures
      2. May be useful as adjunctive treatment

   iii) NSAIDs
      1. Not effective as monotherapy
      2. Most useful when used in combination with TCAs
3. Literature review

### Pooled analysis of two randomized, double-blind, placebo-controlled trials of milnacipran (Savella®) monotherapy in the treatment of FMS (7)

| **Methods** | Data was pooled from two similarly trials with milnacipran (Savella®) 100 and 200 mg/day  
|            | o Study 1: 3 month study with landmark visits at 3 months and 6 months (October 2003 to July 2005)  
|            | o Study 2: 3 month study with a subset of patients that continued treatment out to 6 months (November 2004 to December 2006) |
| **Inclusion Criteria** | Male and female patients age 18 to 70 years  
|            | Met the 1990 American College of Rheumatology classification criteria for FMS  
|            | 24-hour recall VAS intensity recorder at the end of the baseline period  
|            | o 0 “no pain” to 100 “worst possible pain” scale  
|            | o Study 1: ≥ 50  
|            | o Study 2: ≥ 40  
|            | Withdraw from all pharmacologic and nonpharmacologic treatments for FMS was required. |
| **Exclusion Criteria** | Severe psychiatric illness or a current major depression episode as defined my the Mini International Neuropsychiatric Interview  
|            | Active cardiac, pulmonary, hepatic, renal, or immune system disorders |
| **Design** | Four phases: screening and washout, baseline assessment, dose escalation, and stable-dose  
|            | 3 arms: placebo, milnacipran 100 mg/day, or milnacipran 200 mg/day  
|            | Medication administration: blinded, twice daily through the dose-escalation phase and stable dose phase.  
|            | Efficacy assessments: initiation of baseline phase, randomization visit, and study visits.  
|            | Electronic patient experience diary (PED) pain data were collected daily |
| **Outcome Measures** | Patients were considered 2-measure composite responders if they concurrently had:  
|            | o ≥ 30% improvement from baseline in PED VAS 24-hour recall pain score  
|            | o PGIC rating of “very much improved” or “much improved:  
|            | Patients were considered 3-measure composite responders if they concurrently had:  
|            | o The criteria for 2-measure response  
|            | o Improvement in physical function as measured by Short Form 36 Health Survey Component Summary score  
|            | Each component was also assessed separately |
| **Analysis** | Intent to treat |
| **Results** | Baseline Characteristics (Appendix C)  
|            | o 624 placebo vs 623 milnacipran 100mg/day vs 837 milnacipran 200 mg/day  
|            | o Mostly female  
|            | 3 month analysis  
|            | o Composite measure response.  
|            | • Milnacipran consistently out-performed placebo.  
|            | Graph (A) in figure 3 shows the 2-measure composite responders and graph (B) in figure 3 shows the 3-measure composite responders  
|            | Individual components of the composite responder analysis (Table 3)  
|            | Milnacipran consistently outperformed placebo |
| **Limitations** | Exclusion of patients with active immune system disorders and depression makes the results of the trials less externally valid. |
Figure 3: Three month composite responder rates from Geisser et al (7)

Figure 4: Responder rates at 3 months for individual components of composite responder analysis from Geisser, et al (7)
Comparative efficacy and acceptability of amitriptyline (Elavil®) (AMT), duloxetine (Cymbalta®) (DLX) and milnacipran (Savella®) (MLN) in FMS syndrome: a systemic review with meta-analysis (8)

Methods
- Databases searched
- Search criteria
  - Randomized pharmacological placebo-controlled trials until 30 May 2010

Inclusion Criteria
- Randomized controlled trials comparing AMT, DLX, or MLN with placebo
- Trials that included patients diagnosed with FMS of any age

Exclusion Criteria
- Excluded all trials where drugs were combined with other defined treatments

Design

Outcome Measures
- Included studies had to assess at least 1 key domain of FMS and report treatment discontinuation rates
- Discontinuation rates were considered the estimate of treatment acceptability

Analysis
- Non-parametric tests were used for the comparison of continuous variables and chi-squared tests for the comparison of categorical variables.
- Numbers needed to treat (NNT) were calculated using the pooled number of observations
- Tested for heterogeneity

Results
- Efficacy (Appendix D)
  - AMT
    - Significant small effect on pain (3.54 = NNT for 30% reduction) and fatigue
    - Significant moderate effect on sleep
    - No significant effect on Health Related Quality of Life (HRQOL)
  - DLX
    - Small significant effect on pain (8.21= NNT for 30% reduction), sleep, and HRQOL
    - No significant effect on fatigue
  - MLN
    - Significant effects on pain (10.96 = NNT for 30% reduction), fatigue, and HRQOL that were not considered substantial
    - No significant effects on sleep
- Comparative efficacy (Table 5)
  - Pain: AMT > DLX > MLN
  - Sleep disturbances: AMT > DLX > MLN
  - Fatigue: AMT > MLN > DLX
  - Limitations of HRQOL: AMT > DLX > MLN
  - No significant difference in drop-out rate, the surrogate marker for acceptability

Limitations
- As always both a strength and weakness of the study is the fact that it is a meta-analysis
- Similarity assumption for indirect comparisons partially fulfilled
- Some patient characteristics differ significantly
- Methodological quality of AMT studies may be lower.
Table 4: Adjusted relative efficacy and acceptability taken from Hauser et al (8)

<table>
<thead>
<tr>
<th>Comparison (effect estimate)</th>
<th>Adjusted indirect estimates (ratios)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMT vs DLX (95% CI)</td>
</tr>
<tr>
<td>Pain (SMD)*</td>
<td>1.35 (1.10, 1.64)</td>
</tr>
<tr>
<td>Fatigue (SMD)*</td>
<td>5.87 (9.11)</td>
</tr>
<tr>
<td>Sleep (SMD)*</td>
<td>1.80 (1.43, 2.27)</td>
</tr>
<tr>
<td>Quality of life (SMD)*</td>
<td>1.93 (1.50, 2.48)</td>
</tr>
<tr>
<td>30% pain reduction (RR)*</td>
<td>1.24 (1.02, 1.52)</td>
</tr>
<tr>
<td>Total drop-out rate (RR)</td>
<td>0.77 (0.48, 1.25)</td>
</tr>
</tbody>
</table>

*Significant comparisons (95% CIs with lower and upper limit < 1 or > 1
Appendix A: Selected clinical characteristics of patients with current of prior fibromyalgia and controls in phase 1 from Wolf et al. (6)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Current fibromyalgia</th>
<th>Prior fibromyalgia</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>196 (38.1)</td>
<td>67 (13.0)</td>
<td>251 (48.1)</td>
</tr>
<tr>
<td>Widespread pain index (0–19)</td>
<td>11.4 ± 4.4</td>
<td>8.2 ± 5.0</td>
<td>3.8 ± 3.2</td>
</tr>
<tr>
<td>Physician widespread pain index (0–19)</td>
<td>11.4 ± 4.1</td>
<td>7.2 ± 3.9</td>
<td>3.3 ± 2.5</td>
</tr>
<tr>
<td>Widespread pain, % patients</td>
<td>92.9</td>
<td>56.7</td>
<td>31.1</td>
</tr>
<tr>
<td>Widespread pain, % physicians</td>
<td>93.9</td>
<td>59.7</td>
<td>24.3</td>
</tr>
<tr>
<td>Tender point count (0–18)</td>
<td>15.9 ± 2.3</td>
<td>7.9 ± 4.1</td>
<td>2.5 ± 3.0</td>
</tr>
<tr>
<td>ACR 1990 classification criteria positive, % patients</td>
<td>92.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ACR 1990 classification criteria positive, % physicians</td>
<td>93.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ACR 1990 classification positive, % patients or physicians</td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Physician global severity, categorical (0–3)</td>
<td>2.1</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Patient global severity, categorical (0–3)</td>
<td>2.4</td>
<td>1.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Patient symptom count (0–48)</td>
<td>22.9 ± 8.8</td>
<td>18.2 ± 8.4</td>
<td>9.7 ± 8.4</td>
</tr>
<tr>
<td>Physician somatic symptoms (0–3)</td>
<td>2.3 ± 0.7</td>
<td>1.9 ± 0.7</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>HAQ-II score (0–3)</td>
<td>1.3 ± 0.6</td>
<td>1.0 ± 0.7</td>
<td>0.7 ± 0.6</td>
</tr>
<tr>
<td>Patient VAS unrefreshed sleep (0–10)</td>
<td>7.3 ± 2.7</td>
<td>5.2 ± 3.4</td>
<td>3.1 ± 3.0</td>
</tr>
<tr>
<td>Patient VAS sleep (0–10)</td>
<td>6.5 ± 2.8</td>
<td>4.4 ± 3.2</td>
<td>3.3 ± 3.0</td>
</tr>
<tr>
<td>Patient VAS pain (0–10)</td>
<td>6.5 ± 2.3</td>
<td>4.9 ± 2.7</td>
<td>4.1 ± 2.8</td>
</tr>
<tr>
<td>Patient VAS fatigue (0–10)</td>
<td>7.0 ± 2.4</td>
<td>5.0 ± 3.1</td>
<td>3.3 ± 2.9</td>
</tr>
<tr>
<td>Symptom severity scale (0–12)†</td>
<td>8.0 ± 2.6</td>
<td>6.0 ± 2.6</td>
<td>3.3 ± 2.2</td>
</tr>
<tr>
<td>No. of pain medications</td>
<td>3.3 ± 2.3</td>
<td>2.5 ± 1.4</td>
<td>1.9 ± 1.9</td>
</tr>
</tbody>
</table>

* Values are the mean ± SD unless otherwise indicated. ACR = American College of Rheumatology; HAQ-II = Health Assessment Questionnaire II; VAS = visual analog scale.
† Sum of physician somatic symptoms, physician waking unrefreshed, physician cognition, and physician fatigue.

Appendix B: Symptoms reviewed in phase one from Wolfe et al. (6)

- Blurred vision or problems focusing
- Dry eyes
- Ringing in ears
- Hearing difficulties
- Mouth sores
- Dry mouth
- Loss of or change in taste
- Headache
- Dizziness
- Fever
- Chest pain
- Shortness of breath
- Wheezing (asthma)
- Loss of appetite
- Nausea
- Heartburn
- Indigestion or belching
- Pain or discomfort in the upper abdomen (stomach)
- Pain or cramps in the lower abdomen (colon)
- Tender lymph nodes
- Frequent sore throat
- Diarrhea (frequent, explosive watery bowel movements, severe)
- Constipation
- Black or tarry stools (not from iron)
- Vomiting
- Liver problems
- Joint pain
- Joint swelling
- Low back pain muscle pain
- Neck pain
- Weakness of muscles
- Tiredness (fatigue)
- Depression
- Insomnia
- Nervousness (anxiety)
- Seizures or convulsions
- Trouble thinking or remembering
- Easy bruising
- Hives or welts
- Itching rash
- Loss of hair
- Red, white, and blue skin color changes in fingers on exposure cold or with emotional upset
- Sun sensitivity (unusual skin reaction, not sunburn)
- Yellow skin or eyes (jaundice)
- Fluid-filled blisters
- Numbness/tingling/burning swelling of the hands, legs, feet, or ankles (not due to arthritis)
- Irritable bowel syndrome
- Faintness
- Frequent urination
- Painful urination
- Pain, fullness, or discomfort in the bladder
- Region
- Sensitivity to bright lights, loud noises, or odors fatigue severe enough to limit daily activity
Appendix C: Baseline characteristics taken from Geisser et al (7)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 624)</th>
<th>Milnacipran 100 mg/day (n = 623)</th>
<th>Milnacipran 200 mg/day (n = 837)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>50.2 (10.3)</td>
<td>49.7 (10.8)</td>
<td>49.8 (10.8)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>593 (95.0)</td>
<td>600 (96.3)</td>
<td>807 (96.4)</td>
</tr>
<tr>
<td>Male</td>
<td>31 (5.0)</td>
<td>23 (3.7)</td>
<td>30 (3.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>586 (93.6)</td>
<td>583 (93.6)</td>
<td>780 (93.2)</td>
</tr>
<tr>
<td>Other</td>
<td>38 (6.1)</td>
<td>40 (6.4)</td>
<td>57 (6.8)</td>
</tr>
<tr>
<td>Weight, mean (SD), lbs</td>
<td>183.2 (43.4)</td>
<td>179.9 (41.9)</td>
<td>180.3 (43.2)</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>30.9 (7.1)</td>
<td>30.4 (7.0)</td>
<td>30.5 (7.1)</td>
</tr>
<tr>
<td>FMS duration, mean (SD), years</td>
<td>8.4 (7.9)</td>
<td>8.1 (7.4)</td>
<td>7.7 (7.1)</td>
</tr>
<tr>
<td>BDI score, mean (SD), range 0-63</td>
<td>13.9 (9.2)</td>
<td>13.5 (8.3)</td>
<td>14.4 (8.6)</td>
</tr>
<tr>
<td>VAS 24-hour morning recall pain score, mean (SD), range 0-100</td>
<td>66.7 (12.9)</td>
<td>65.9 (12.9)</td>
<td>67.1 (13.0)</td>
</tr>
</tbody>
</table>

BDI = Beck Depression Inventory; BMI = body mass index; SD = standard deviation; VAS = visual analog scale

Appendix D: Effect sizes of amitriptyline (AMT), duloxetine (DLX) and MLN on outcome variables taken from Hauser et al (8)
References


