Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome
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CRD summary
The authors concluded that there was evidence of the short-term (up to six months) efficacy of duloxetine, milnacipran and pregabalin in fibromyalgia syndrome; the drugs differed in their effects on fibromyalgia syndrome domains and side-effects. The conclusions about the relative efficacy of drugs were not based on direct comparisons and may not be definitive.

Authors' objectives
To compare the efficacy and side-effects of duloxetine, milnacipran and pregabalin for the treatment of fibromyalgia syndrome.

Searching
MEDLINE, SCOPUS and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to May 2009. Information was provided about the search strategy. Unpublished data were sought from websites of the United States Food and Drug Administration (FDA), National Institutes of Health (NIH) and Pharmaceutical Research and Manufacturers of America. Reference lists of included studies, prescribing information of the FDA and Centre for Drug Evaluation and Research reviews were searched.

Study selection
Eligible studies were randomised controlled trials (RCTs) that directly compared at least two of the drugs in question (duloxetine, milnacipran and pregabalin) or compared any of these drugs with a pharmacological placebo. Uncontrolled open-label extension studies of any of the specified drugs were eligible. Studies had to assess at least one key domain of fibromyalgia syndrome (pain, sleep, fatigue, depressed mood, health-related quality of life and harms). Only data published in full papers or available from one of the public databases searched were included.

All the included studies were of patients aged 18 years or more diagnosed with fibromyalgia syndrome using American College of Rheumatology criteria. Some patients had comorbid major depressive disorder. Patients were allowed other medication. All studies excluded patients with unstable somatic diseases; studies of individual drugs had specific exclusion criteria. Most participants were American. Patients were recruited by referral from physicians and advertisements. Median age was 49 years (range 47 to 51). Ninety per cent of participants Caucasian. Ninety-five per cent of participants were women. Studies used various instruments to assess different outcomes.

Two reviewers independently selected studies. Disagreements were resolved by consensus and the help of a third reviewer if required.

Assessment of study quality
Validity was assessed using the 11 items described by van Tulder et al. Studies were classed as high (score 8 to 11), moderate (5 to 7) or low (score 1 to 4) quality.

The authors did not state how many reviewers assessed validity.

Data extraction
Relative risks (RRs) were calculated for dichotomous data and standardised mean differences (SMDs) were calculated for continuous data from means and standard deviations or change scores. Drug sponsors, medical information departments and first authors of published studies were contacted for missing data.

Two reviewers independently extracted data. Disagreements were resolved by consensus with the help of a third
reviewer if required.

**Methods of synthesis**

Pooled relative risks with 95% confidence intervals (CIs) were calculated for dichotomous data using a Mantel-Haenszel random-effects model. Pooled SMDs (Hedges adjusted g) and 95% CIs were calculated for continuous data, also using a random-effects model.

Statistical heterogeneity was assessed using $I^2$. $I^2$ was used to indicate the amount of heterogeneity explained by subgroup differences. Numbers needed to treat (NNT) and numbers needed to harm (NNH) were calculated.

Drugs were compared indirectly using the adjusted indirect analysis method described by Bucher et al. in which relative risks are adjusted by results for their comparison with placebo.

Where more than 10 RCTs were available for each drug, potential for publication bias was assessed using a funnel plot.

**Results of the review**

Seventeen studies were included in the review (4,508 patients received treatment and 1,880 were controls). Six studies were open-label.

Eleven RCTs were included in meta-analyses (6,388 patients). These included four RCTs that evaluated duloxetine (n=1,411 randomised), three RCTs that evaluated milnacipran (n=2,213 randomised) and four RCTs that evaluated pregabalin (n=2,768 randomised). Sample size ranged from 125 to 1,200. Median duration of the randomised phase was 24 weeks (range six to 28 weeks). The median percentage of patients randomised was 55%. All studies were initiated by pharmaceutical companies. All studies were high quality (van Tulder scores of 8 or 9).

The median percentage of patients who completed the studies was 64% (range 55% to 78%) for active drugs and 68% (range 50% to 77%) for placebo.

**Compared with placebo:** All three drugs were more effective than placebo, except duloxetine for fatigue, milnacipran for sleep disturbance and pregabalin for depressed mood. Results were reported in the review.

**Comparative efficacy and harms:** There was no significant difference between duloxetine, milnacipran and pregabalin in the proportion of patients with more than 30% pain relief and for withdrawals due to adverse events.

Compared to milnacipran, duloxetine and pregabalin significantly reduced pain (SMD 1.74, 1.68 to 1.80 for duloxetine versus milnacipran and SMD 0.70, 95% CI 0.58 to 0.82 for milnacipran versus pregabalin) and sleep disturbance (SMD 6.20, 95% CI 6.05 to 6.35 for duloxetine versus milnacipran and SMD 0.84, 95% CI 0.69 to 0.99 for milnacipran versus pregabalin).

Duloxetine significantly improved depressed mood compared to milnacipran (SMD 2.45, 95% CI 2.32 to 2.58) and pregabalin (SMD 27.0, 95% CI 26.83 to 27.17).

Milnacipran and pregabalin significantly improved fatigue compared to duloxetine (SMD 0.77, 95% CI 0.67 to 0.87 for duloxetine versus milnacipran and SMD 0.62, 95% CI 0.52 to 0.72 for duloxetine versus pregabalin).

Duloxetine and milnacipran significantly increased headache and nausea compared to pregabalin (RR of headache 2.24, 95% CI 1.83 to 2.65 for duloxetine versus pregabalin and RR of headache 1.81, 95% CI 1.48 to 2.14 for milnacipran versus pregabalin) and (RR of nausea 3.25, 95% CI 2.13 to 4.37 for duloxetine versus pregabalin and RR of nausea 1.90, 95% CI 1.37 to 2.43 for milnacipran versus pregabalin).

Duloxetine significantly increased diarrhoea compared to milnacipran (RR 2.21, 95% CI 1.64 to 2.78) and pregabalin (RR 2.01, 95% CI 1.23 to 2.99).

Duloxetine significantly reduced health-related quality of life (HRQoL) compared to milnacipran (SMD1.47, 95% CI
1.29 to 1.65) and milnacipran significantly reduced HRQoL compared to pregabalin (SMD 0.44, 95% CI 0.28 to 0.60).

Other results were presented in tables. Results of the open uncontrolled trials were reported.

The small number of studies precluded investigation of potential publication bias.

**Authors' conclusions**
There was evidence of short-term (up to six months) efficacy of duloxetine, milnacipran and pregabalin in fibromyalgia syndrome. Differences with regard to the occurrence of key symptoms of fibromyalgia syndrome and to drug-specific adverse events may be relevant for the choice of medication.

**CRD commentary**
The review question was clearly stated. Inclusion criteria were appropriately defined. Several relevant sources were searched and attempts were made to minimise publication bias. It was unclear whether any attempts were made to minimise language bias. Validity was assessed, but only aggregate scores were presented. Methods were used to minimise reviewer errors and bias during study selection and data extraction; it was not clear whether similar steps were taken for the validity assessment. In the absence of head-to-head comparison of drugs, indirect comparison methods were used. The comparability of studies was discussed and some limitations of this method of analysis were discussed. Statistical heterogeneity was not reported for the indirect analyses. Some studies had high drop-out rates and this may have influenced results. The authors discussed that patients with comorbidities were excluded and so findings may not be applicable to other patient groups.

The conclusions about the relative efficacy of drugs were not based on direct comparisons and may not be definitive.

Duloxetine, milnacipran and pregabalin are the subject of contraindications, warnings and recommendations from the FDA.

**Implications of the review for practice and research**
**Practice:** The authors stated that clinicians selecting drug treatment should take into account the specific safety warnings, contraindications, common comorbidities, patient's preferences and differences between drugs. Drugs should be started at low doses and their effects monitored.

**Research:** The authors did not state any implications for research.

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