

Evidence Based Practice Critically Appraised Topic

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**Case Scenario:**

A 38 year old woman presents with a 4 year history of widespread body pain. The pain began after a motor vehicle accident and was initially limited to her neck. The pain has progressed since the incident, and she now complains of hurting all over, all the time. She does not have any joint swelling or systemic symptoms. She does not sleep well and reports fatigue. She is otherwise healthy. Physical exam reveals a well appearing woman with normal musculoskeletal exam, except for the presence of tenderness in 12 out of 18 fibromyalgia tender points. Routine laboratory testing is normal.

**Clinical Question:**

Do adults with fibromyalgia experience better pain control when enrolled in an exercise training program compared to treatment with duloxetine?

**Articles:**

Busch, A. J., Barber, K. A., Overend, T. J., Peloso, P. M. J., and Schachter, C. L. (2008). Exercise for treating fibromyalgia syndrome (review). *The Cochrane Library*, 4, 1-77.

Lunn, M. P. T., Hughes, R. A. C. and Wiffen, P. J. (2010). Duloxetine for treating painful neuropathy or chronic pain (review). *The Cochrane Library*, 3, 1-79.

**Critical Review of Study:**

Busch et al. (2008) completed a Level 1a systematic review of randomized clinical trials that compared an intervention that included an exercise component with an untreated control or a non-exercise intervention. Studies were included if the authors used words such as randomly, random or randomization to describe the method of assignment of subjects to groups. Lunn, Hughes, and Wiffen (2010) completed a meta-analysis providing Level 1a evidence which included only double blind randomized trials of duloxetine for treating painful neuropathy or chronic pain conditions. Duloxetine was to have been administered for a minimum of eight weeks.

**Methodology**

Busch et al. (2008) used a variety of published criteria for the diagnosis of fibromyalgia. Although there were differences between the diagnostic criteria, all criteria were considered acceptable and comparable. All studies compared, allowed for exclusion of individuals with medical conditions that exercise could be contraindicated or unsafe under unmonitored conditions. Exercise was defined as the “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (ASCM, 2001). Outcome measures did not form part of the inclusion criteria for the review. The outcome measures were grouped into six constructs which included pain, global well-being or perceived improvement in fibromyalgia symptoms, physical function, tenderpoints, depression, and fatigue/sleep. There were a total of 2276 subjects with the confirmed diagnosis of fibromyalgia across the studies; 1264 subjects were assigned to exercise interventions. The average sample

size for the smallest experimental group was 24.7 (SD=16.4, min-max: 5-80) for the 34 original studies. Mean age in the studies ranged from 27.5 to 60.2 years in 34 studies. For the 2197 subjects for whom gender was reported, 96.4% were female. Nineteen studies involved only females; twelve examined both males and females, with females in the majority; and the remaining three studies did not specify the gender of participants. Few studies used participation in regular physical activity prior to study entry as an exclusion criterion.

Lunn et al. (2010) included double blind randomized trials of duloxetine for treating painful neuropathy or chronic pain conditions. Those included to participate had any form of painful peripheral neuropathy or chronic pain. All formulations and doses of duloxetine in comparison with placebo or other controls were included in the review. The primary outcome was short-term (up to 12 weeks) improvement of pain compared with baseline using validated scales of pain intensity or pain relief. Both visual analogue and categorical scales were accepted in the review.

### Results

Busch et al. (2008) looked at a total of 2276 subjects across the 34 included studies; 1264 subjects were assigned to exercise interventions. The 34 studies comprised 47 interventions that included exercise. Effects of several disparate interventions on global well-being, selected fibromyalgia signs and symptoms, and physical function in individuals with fibromyalgia were summarized using standardized mean differences (SMD). There is moderate quality evidence that aerobic-only exercise training at recommended intensity levels has positive effects global well-being (SMD 0.49, 95% CI: 0.23 to 0.75) and physical function (SMD 0.66, 95% CI: 0.41 to 0.92) and possibly on pain (SMD 0.65, 95% CI: -0.09 to 1.39) and tender points (SMD 0.23, 95% CI: -0.18 to 0.65). Strength and flexibility remain under-evaluated.

Lunn et al. (2010) included six trials and identified 2220 participants. Three studies included participants with painful diabetic neuropathy and three treated participants with fibromyalgia. Duloxetine at 60 mg daily is effective in treating painful diabetic peripheral neuropathy in the short-term to 12 weeks with a risk ratio (RR) for 50% pain reduction at 12 weeks of 1.65 (95% confidence interval (CI) 1.34 to 2.03), number needed to treat (NNT) 6 (95% CI 5 to 10). Duloxetine at 60 mg daily is also effective in fibromyalgia over 12 weeks (RR 50% reduction in pain 1.57, 95% CI 1.20 to 2.06; NNT 8, 95% CI 5 to 17) and 28 weeks (RR 1.58, 95% CI 1.10 to 2.27). Adverse events were common in both treatment and placebo arms but more common in the treatment arm with a dose dependent effect. Most side effects were minor, but 16% of participants stopped the drug due to side effects. Serious adverse events were rare.

### **Clinical Bottom Line:**

Busch et al. (2008) review established there is 'gold' level evidence that supervised aerobic exercise training has beneficial effects on physical capacity and fibromyalgia symptoms. Strengths of Busch et al. include use of random controlled trials, a large number of participants and 47 different interventions for exercise were evaluated. Weakness of the meta-analysis indicates a need for further studies on muscle strengthening and flexibility. Research on the long-term benefit of exercise for fibromyalgia is also needed. Lunn et al., (2010) found moderately strong evidence that duloxetine 60 mg and 120 mg daily are efficacious for treating pain in

diabetic peripheral neuropathy and fibromyalgia but 20 mg daily is not. Strengths of this meta-analysis include a large number of participants over 6 trials, minor side effects were common at therapeutic doses but serious side effects were rare. Three weaknesses of the meta-analysis are no direct comparisons of duloxetine with other antidepressants, it is not clear whether the use of duloxetine is cost effective when compared to the other drugs already in use and it did not focus on fibromyalgia pain specifically.

These studies demonstrate exercise may have more beneficial effects on treating pain in fibromyalgia patients. Busch et al. established there is evidence that exercise training is beneficial for those who suffer pain from fibromyalgia symptoms specifically. Although there is strong moderately strong evidence that duloxetine is efficacious for treating neuropathic and fibromyalgia pain the effects of the medication may be limited to a time frame of 12-28 weeks. Continuous exercise is most likely better in the long term for the treatment of fibromyalgia pain in adults.

### **Implications for Practice:**

A once-daily aerobic fitness program with intensity titrated to the patient's threshold for pain and fatigue promotes adherence and the likelihood of improved outcome measures. Aerobic exercise should be initiated during a period of relative symptom stability and concurrent with medical interventions. Some experts have recommended providers use motivational interviewing to overcome patients' resistance to exercise and build self-efficacy (Huynh, Yanni, & Morgan, 2008). Patient education should work to build confidence, supporting the belief that exercise will improve symptoms. However, patients should be informed that improvement may take many months and symptoms, such as fatigue and pain, may initially worsen if the patient is not particularly well conditioned (Huynh et al., 2008). Patients who have failed exercise programs multiple times because of exacerbation of pain or fatigue may benefit from a supervised exercised program with a physical therapist (Huynh et al., 2008).

SNRIs, like Duloxetine, are the first and second line pharmacological choices for patients with fibromyalgia (Huynh et al., 2008). They lack the high side effect profile and potential drug interactions of tricyclic antidepressants. This suggests that blockade of both serotonin and norepinephrine reuptake is more effective than blockade of either neurotransmitter alone in the treatment of fibromyalgia (Huynh et al., 2008). More evidence is needed, but encouraging results reviewed in Lunn et al. (2010) suggest efficacy and make SNRIs a reasonable choice for symptom control.

If patients are looking for a non-pharmacological way of managing their fibromyalgia, aerobic exercise has been proven to be truly effective and possibly more so than with pharmacological management. It is truly appropriate to recommend exercise as a first-line treatment to adults with fibromyalgia.

### Resources

American College of Sports Medicine. (2001). ACSM's resource manual for guidelines for exercise testing and prescription. 4<sup>th</sup> ed. Lippincott, Williams, & Wilkins.

Huynh, C. N., Yanni, L. M., and Morgan, L. A. (2008). Fibromyalgia: Diagnosis and management for the primary healthcare provider. *Journal of Women's Health, 17*(8), 1379-1387.