

Otto M, Bach FW et al. Escitalopram in painful polyneuropathy: A randomized, placebo-controlled, cross-over trial. *Pain* 2009;139:275-283.

Design: Randomized crossover trial

Population/sample size/setting:

- 37 patients (29 men, 12 women, median age 62) who completed a 14 week crossover trial of escitalopram for painful neuropathy of various etiologies in a neurology department in Denmark
- The etiologies were: diabetes, 19; idiopathic, 14, alcoholic, 4; monoclonal gammopathy, 1, connective tissue disease, 1, hypothyroidism, 2
- Eligibility was based on symptoms of polyneuropathy (distal bilateral sensory disturbances and decreased tendon reflexes) for at least 6 months, confirmed by electrophysiological testing or by quantitative sensory testing, with a median pain score of at least 4 on a scale from 0-10 during a week when not taking pain medication
- Exclusion was based on causes of pain other than polyneuropathy, previous allergic reactions to escitalopram or citalopram, terminal illness, pregnancy/lactation, or concurrent treatment with antidepressants, MAO inhibitors, or anticonvulsants

Main outcome measures:

- After a week of observation, the patients entered a crossover trial taking either escitalopram or placebo during the first 6 weeks, with a washout period of 2 weeks, followed by a second 6 week period taking the drug not taken in the first period
- 47 patients were randomized to enter the trial, 25 to take placebo first, and 22 to take escitalopram first
- The starting dose of escitalopram was 10 mg/d, and was increased to 20 mg/d after the first week
- 10 patients withdrew before trial completion: in the placebo/escitalopram (P/E) group, 2 withdrew while taking placebo and 4 while taking escitalopram; in the escitalopram/placebo (E/P) group, 2 withdrew while taking escitalopram and 2 while taking placebo
- Based on the Major Depression Inventory (MDI), the patients were dichotomized into depressed and non-depressed subgroups for later analysis to determine if depression had an effect on the treatment response
- Pain relief was characterized as complete, good, moderate, slight, none, or worse; patients saying their pain relief was moderate or better were classified as "responders"
- There were more responders taking escitalopram (n=11) than placebo (n=3); no patient reported complete pain relief at any period in the trial
- No period or carryover effects were observed
- The SF-36 was used as a secondary measure of treatment effect; all of the SF-36 subscales were unaffected by escitalopram compared to placebo

- Non-depressed patients responded to escitalopram more than to placebo, suggesting to the authors that depression is not a primary pathway for the action of escitalopram
- Ratings of adverse effects did not differ between escitalopram and placebo
- 81% of responders reported at least 1 adverse effect, but only 40% of non-responders reported an adverse effect

Authors' conclusions:

- There is a weak analgesic effect from escitalopram; with the mean pain reduction being only 1 point on an 11 point scale
- It is possible that the small sample size accounts for the small observed effect
- There may be mixed actions of descending serotonin pathways on pain, depending on the receptor with which serotonin interacts; the 5-HT-3 receptor may facilitate pain, even if other receptors inhibit pain
- A clinically relevant effect was seen in too few patients to recommend escitalopram as a standard treatment for polyneuropathy pain

Comments:

- The MDI was used to dichotomize patients into depressed and non-depressed groups, but the cutoff score is not clear, and there are probably too few patients to have a robust subgroup analysis
- Randomization and concealment of allocation are adequate
- Although no formal test of blinding was done, the authors may have a plausible reason to infer from the equal distribution of adverse effects that unblinding was not a major source of bias
- The authors interpret the frequency of adverse effects among responders (81%) compared to non-responders (40%) as an odds ratio of 6.7 using logistic regression
- This is a misinterpretation of an odds ratio, which inflates the relative risk when an event is common (occurring in 40% of the "low risk" group); the actual ratio is only 2
- The type of logistic regression is not specified, but because the subjects were their own controls, the observations were matched, and a conditional logistic regression model would be called for
- The authors calculated a number needed to treat (NNT) of 6.8 for escitalopram to produce a favorable response, and interpret this as evidence of a weak effect of escitalopram
- This may be an unduly pessimistic interpretation of the NNT; in many contexts, an NNT of 6.8 is interpreted as evidence of fairly good effectiveness of a drug
- Nevertheless, there are grounds for the authors' conclusion that escitalopram is not likely to be considered as a standard treatment for painful polyneuropathy

Assessment: Adequate for evidence that escitalopram is unlikely to be highly effective for the treatment of painful polyneuropathy