

Oral iron therapy reduced unexplained fatigue in nonanemic women with serum ferritin levels $\leq 50 \mu\text{g/L}$

Verdon F, Burnand B, Fallab Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. *BMJ*. 2003;326:1124-7.

QUESTION

Is iron therapy effective for nonanemic women with unexplained fatigue?

DESIGN

Randomized (allocation concealed*), blinded {patients, clinicians, data collectors, and outcome assessors}†, * placebo-controlled trial with 1 month follow-up.

SETTING

An academic primary care center and 8 private general practices in western Switzerland.

PATIENTS

144 women 18 to 55 years of age whose primary reason for consulting was fatigue. Exclusion criteria were anemia (hemoglobin $< 117 \text{ g/L}$), other obvious physical or psychiatric causes of fatigue, or the chronic fatigue syndrome. 136 patients (94%) were included in the 1-month analysis (mean age 35 y).

INTERVENTION

75 women were allocated to oral long-acting ferrous sulfate (Tardyferon, Robapharm,

Boulogne, France), 80 mg/d for 4 weeks, and 69 women were allocated to matching placebo.

MAIN OUTCOME MEASURES

Main outcome was perceived level of fatigue (10-point visual analogue scale [VAS] ranging from 1 = no fatigue at all to 10 = very severe fatigue). Secondary outcomes included adherence to treatment.

MAIN RESULTS

Analysis was by intention to treat. 115 women (85%) had serum ferritin levels $\leq 50 \mu\text{g/L}$, and 69 women (51%) had levels $\leq 20 \mu\text{g/L}$. Mean decrease in the overall intensity of fatigue from baseline to 1 month was greater in the ferrous sulfate group than in the placebo group (Table). However, subgroup analysis showed that only women with

ferritin levels $\leq 50 \mu\text{g/L}$ had decreased fatigue intensity. The groups did not differ for compliance rates (95% vs 98%, $P = 0.25$)

CONCLUSIONS

Oral iron therapy improved perceived level of fatigue more than did placebo in nonanemic women with unexplained fatigue. It was unclear if improvement occurred in women with serum ferritin levels $> 50 \mu\text{g/L}$.

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*See Glossary.

†Information provided by author.

Oral ferrous sulfate vs placebo for women with unexplained fatigue†

Outcomes	Ferrous sulfate	Placebo	Mean difference (95% CI)
Decrease in overall fatigue intensity from baseline to 1 mo	-1.82	-0.85	0.97 (0.32 to 1.62)

†CI defined in Glossary.

COMMENTARY

The small randomized controlled trial by Verdon and colleagues raises several questions.

First, are the results biologically plausible? Iron is an important component in a number of proteins involved in oxidative processes and muscle functioning, and a recent review of animal and human research found some evidence that iron deficiency without anemia may lead to decreased physical functioning (1). Maximum oxygen consumption ($\text{VO}_{2\text{max}}$) is decreased in nonanemic women with low iron stores and improves with 6 weeks of iron supplementation (2).

Are the results clinically meaningful? The authors did not report improvement rates, so numbers needed to treat cannot be calculated. The reported 0.97-point decrease on a 10-point VAS is less than the 1.1 to 1.3 points found to represent the minimal clinically appreciable difference when a VAS was used to measure disability (3) or pain (4).

How long should the treatment continue? Would more than 1 month of therapy lead to more impressive results?

Is there a target ferritin level? The authors' subgroup analysis is somewhat questionable, since only 21 women in their sample had ferritin levels $> 50 \mu\text{g/L}$.

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