Oral iron therapy reduced unexplained fatigue in non-anaemic women with serum ferritin concentrations $\leq 50 \mu\text{g/l}$

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.

Clinical impact ratings GP/FP/Primary care ★★★★★☆ IM/Ambulatory care ★★★★★☆

Q Is iron therapy effective for non-anaemic women with unexplained fatigue?

METHODS

Design: randomised, placebo controlled trial.

Allocation: concealed.*

Blinding: blinded (patients, clinicians, data collectors, and outcome assessors)†.*

Follow up period: 1 month.

Setting: an academic primary care centre and 8 private general practices in western Switzerland.

Patients: 144 women 18–55 years of age (mean age 35 y, based on n = 136) whose primary reason for consulting was fatigue. Exclusion criteria: anaemia (haemoglobin concentration $< 117 \text{ g/l}$), other obvious physical or psychiatric causes of fatigue, or chronic fatigue syndrome.

Interventions: oral, long acting ferrous sulphate (Tardyferon, Robapharm, Boulogne, France), 80 mg/day, for 4 weeks (n = 75) or matching placebo (n = 69).

Outcomes: 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.

Patient follow up: 94%.

*See glossary.
†Information provided by author.

MAIN RESULTS

Analysis was by intention to treat. 115 women (85%) had serum ferritin concentrations $\leq 50 \mu\text{g/l}$, and 69 women (51%) had concentrations $\leq 20 \mu\text{g/l}$. Mean decrease in the overall intensity of fatigue from baseline to 1 month was greater in the ferrous sulphate group than in the placebo group (table). However, subgroup analysis showed that only women with ferritin concentrations $\leq 50 \mu\text{g/l}$ had decreased fatigue intensity. The groups did not differ for compliance rates (95% v 98%, $p = 0.25$).

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Source of funding: Robapharm.

CONCLUSIONS

Oral iron therapy improved perceived level of fatigue more than placebo in non-anaemic women with unexplained fatigue. It was unclear if improvement occurred in women with serum ferritin concentrations $> 50 \mu\text{g/l}$.

Abstract and commentary also appear in *ACP Journal Club*.

Oral ferrous sulphate v placebo for women with unexplained fatigue*

Outcome	Ferrous sulphate	Placebo	Mean difference (95% CI)
Decrease in overall fatigue intensity from baseline to 1 month	–1.82	–0.85	0.97 (0.32 to 1.62)

*CI defined in glossary.

Commentary

The small randomised controlled trial by Verdon *et al* raises several questions.

Firstly, 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 anaemia may lead to decreased physical functioning.¹ Maximum oxygen consumption ($\text{VO}_{2\text{max}}$) is decreased in non-anaemic 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 disability³ 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 concentration? The authors' subgroup analysis is somewhat questionable, since only 21 women in their sample had ferritin concentrations $> 50 \mu\text{g/l}$.

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- Haas JD, Brownlie T 4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *J Nutr* 2001;**131**:676S–88S.
- Brownlie T 4th, Utermohlen V, Hinton PS, *et al.* Marginal iron deficiency without anemia impairs aerobic adaptation among previously untrained women. *Am J Clin Nutr* 2002;**75**:734–42.
- Iyer LV, Haley SM, Watkins MP, *et al.* Establishing minimal clinically important differences for scores on the pediatric evaluation of disability inventory for inpatient rehabilitation. *Phys Ther* 2003;**83**:888–98.
- Todd KH, Funk KG, Funk JP, *et al.* Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996;**27**:485–9.