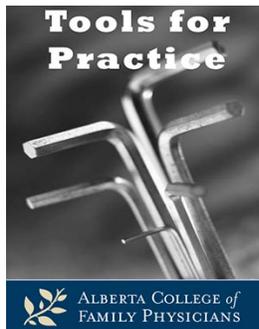


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Iron Supplementation in Non-Anemic Women with Unexplainable Fatigue: Another Tired Theory?

Clinical Question: Is iron supplementation a reasonable option in treating non-anemic, menstruating women with unexplainable fatigue?

Evidence:

Three small but high-quality randomized control trials (RCT) of menstruating non-anemic women (mean age mid-30s) with unexplained fatigue.

- 198 women with serum ferritin $<50 \mu\text{g/L}$, received oral ferrous sulfate (80 mg elemental iron) or placebo daily x12 weeks.¹
 - Iron statistically significantly improved fatigue score, 3.5 points (95% confidence interval (CI) 0.3 to 6.7) versus placebo (40 point scale)
 - No significant effects on quality of life, depression or anxiety
- 144 women received oral ferrous sulfate (80 mg elemental iron) or placebo daily x4 weeks.²
 - Iron statistically significantly improved fatigue score, 0.97 points (CI 0.32-1.62) versus placebo (10 point scale)
 - Subgroup analysis suggest women with serum ferritin $>50 \mu\text{g/L}$ do not benefit
- 90 women with serum ferritin $<50 \mu\text{g/L}$, received intravenous 200 mg iron or placebo x4 doses in 2 weeks, then followed x 12 weeks.³
 - Mean change in fatigue score (0.4 on a 11 pt scale) was not statistically significant, however
 - Significantly more patients reported "slight (or better) improved fatigue" with iron on a different fatigue questionnaire ($p=0.006$)
 - 63% in iron group versus 34% placebo, Number Needed to Treat (NNT) 4

Context:

- Interpretation is challenged by
 - Each study using multiple and differing scales,
 - Small changes in scales with no discussion of, or planning for, minimally important clinical differences.

- One study¹ later⁴ provided the number of patients reaching cut-offs of uncertain relevance: none were significant (If adequately powered, NNT might be 10).
- When reported, adverse events were more common in the iron group; ^{1,3} significantly so in one study (21% versus 6%; NNH 7) including nausea, chills and headache.³

Bottom-line: In female non-anemic patients with low ferritin (<50 µg/L) who have unexplained fatigue there is some weak evidence (at high risk of bias) of small benefit from iron supplementation. If real, at best 1 in 4 (to 1 in 10) may have slight improvement in fatigue, with 1 in 7 having adverse events.

Authors: Daniel McKennitt MD, G. Michael Allan MD CCFP

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