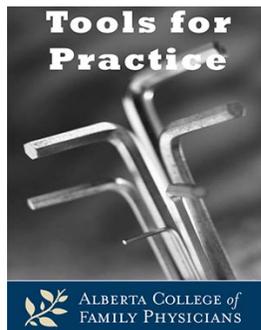


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Reviewed: August 3, 2016
Evidence Updated: New trial; Context updated
Bottom Line: Minor change
First Published: December 10, 2012



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

Clinical Question: Is iron supplementation a reasonable option in treating non-anemic iron-deficient women with unexplained fatigue?

Bottom Line: In female patients with iron deficiency without anemia who have unexplained fatigue, weak evidence suggests small benefit from iron supplementation. If real, about one in four to ten may have improvement in fatigue.

Evidence: Four Randomized Controlled Trials (RCTs) of menstruating non-anemic women (mean age mid-30s) with unexplained fatigue.

- 294 women with serum ferritin $<50 \mu\text{g/L}$,¹ intravenous iron 1000 mg or placebo x1 dose, followed x8 weeks.
 - Iron statistically significantly improved fatigue score by 0.8 points versus placebo (22-point scale).
 - More patients reported $\geq 50\%$ improvement in their fatigue with iron: 33.3% versus 16.4% with placebo, Number Needed to Treat (NNT)=6.
 - Adverse events: Iron 57.2% versus placebo 49% ($p=0.16$).
- 198 women with serum ferritin $<50 \mu\text{g/L}$,² oral ferrous sulfate (80 mg elemental iron) or placebo daily x12 weeks.
 - Iron statistically significantly improved fatigue score by 3.5 points versus placebo (40-point scale).
 - No significant effects on quality of life, depression or anxiety.
 - Adverse events: Iron 34.3% versus placebo 25% ($p=0.20$).
- 144 women,³ oral ferrous sulfate (80 mg elemental iron) or placebo daily x4 weeks
 - Iron statistically significantly improved fatigue score by 0.97 points versus placebo (10-point scale).
 - In subgroup analysis, only benefit if serum ferritin $<50 \mu\text{g/L}$.
- 90 women with serum ferritin $<50 \mu\text{g/L}$,⁴ intravenous iron 200 mg or placebo x4 doses in 2 weeks, followed x12 weeks.
 - No statistically significant difference in fatigue score.

- However, significantly more patients reported “slight or better improvement in fatigue” with iron on a different fatigue questionnaire.
 - Iron 63% versus placebo 34%, NNT=4.
- Adverse events: Iron 53% versus placebo 66%.

Context:

- Interpretation is challenged by:
 - Each study using multiple and differing scales.
 - High placebo response.
 - Small changes in scales with no validated minimal clinically important differences.
 - One study² later⁵ provided the number of patients reaching cut-offs of uncertain relevance: None significant (if adequately powered, NNT might be ~10).
- Cost: Oral iron costs \$20 for a year’s supply;⁶ one 1000-mg dose of intravenous iron costs ~\$300-450.⁷

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