Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: a randomized controlled trial

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Abstract
The true benefit of iron supplementation for nonanemic menstruating women with fatigue is unknown. We studied the effect of oral iron therapy on fatigue and quality of life, as well as on hemoglobin, ferritin and soluble transferrin receptor levels, in nonanemic iron-deficient women with unexplained fatigue.

Reference


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The prevalence of fatigue ranges from 14% to 27% among patients in primary care. In addition, 1%–2% of visits to general practices are because of fatigue, and women are three times more likely than men to mention fatigue. Unexplained fatigue can be caused by iron deficiency. Verdon and coauthors found an improvement in fatigue following iron supplementation in nonanemic women with unexplained fatigue. However, the hemoglobin levels of these patients were not available, which may have contributed to the ongoing debate about the appropriateness of reference limits defining anemia in women. Thus, the effectiveness of iron supplementation in nonanemic menstruating women with major fatigue without an obvious clinical cause is unknown. Our main objective was to test the hypothesis that oral iron therapy for a short period may improve fatigue, hemoglobin, iron stores and quality of life in menstruating nonanemic women whose ferritin levels are below 50 µg/L. Our secondary objective was to evaluate whether this effect is dependent on the initial levels of hemoglobin, ferritin or transferrin saturation.

Methods

Design
We performed a 12-week multicentre, double-blind, placebo-controlled, parallel group, pragmatic randomized trial with a 1:1 allocation ratio.

Setting and participants
We asked general practitioners from 44 private practices in France to invite women who presented with fatigue to participate in this study. To be eligible, the following criteria had to be met: (a) be menstruating women, (b) be between 18 and 50 years old, (c) report considerable fatigue (> 6 on a 1–10 Likert scale) without obvious clinical causes, (d) not have anemia.
treatments were identical in appearance and among nonanemic people. The iron and placebo taste, and the dose regimens were the same.

change in red blood cell indices, particularly
tocol no. L00008CP301). All patients signed an
Saint-Germain-en-Laye) before its initiation (pro-
Random ization and interventions
The clinical pharmacy department of the sponsor
informed consent form before inclusion.

Randomization and interventions
The clinical pharmacy department of the sponsor (Pierre Fabre) generated a simple random alloca-
tion sequence without restriction. This list was
computer generated by use of an internal software
program at Pierre Fabre, which was created in
accordance with their Information Technology
sequence randomly designated 360 consecutive
entries to receive either iron or placebo in a 1:1
cut. The clinical pharmacy service
remained concealed to patients, general practition-
ers, caregivers and principle investigators until the
end of the trial. During the analyses, the statisti-
cian remained blinded as to what treatment each
group received. The clinical pharmacy service
was the sole possessor of the randomization list
during the study period until the database was
locked. The coding of groups was determined by
the pharmacy after the analyses were complete.

Participants were instructed to take orally
either 80 mg/d prolonged-release ferrous sulfate
(Tardyferon; Pierre Fabre Médicament,
Boulogne, France) or placebo before or after
meals for 12 weeks. The length of the treatment
period was justified on a physiologic basis
because more than one month is needed to
enlarge the erythropoietic marrow and obtain a
change in red blood cell indices, particularly
among nonanemic people. The iron and placebo
treatments were identical in appearance and
taste, and the dose regimens were the same.

Outcomes and follow-up
The primary outcome was the level of fatigue
perceived by patients. We assessed fatigue at
baseline and after 12 weeks by use of the Cur-
rent and Past Psychological Scale (le question-
naire de la fatigue de Pichot et Brun) fatigue
score, which ranges from 0 to 40 points." This
questionnaire is a validated 24-item self-admin-
istered questionnaire with three subscales
(fatigue, anxiety and depression), each with eight
items. We also examined levels of depression
and anxiety as additional outcomes. Each item
was scored on a five-point Likert scale. Sec-
ondary outcomes were other measurements of
fatigue, assessed by use of the Multidimensional
Assessment of Fatigue score,10 which ranges
from 0 to 50 points, and the vitality item from
the short-form of the Self-Reported Health Ques-
tionnaire (SF-12),11 which ranges from 0 to 5
points. We also assessed the effects on quality of
life using the entire SF-12 scale and the entire
Current and Past Psychological Scale.

Blood samples for each patient were sent
from a local laboratory to a central laboratory
seven days before inclusion and at 6 and 12
weeks. Thyroid stimulating hormone, C-reactive
protein, hemoglobin, ferritin, red blood cell
count, mean corpuscular volume, hematocrit,
soluble transferrin receptor and transferrin satu-
ratation were measured.

Patients were asked about any adverse reac-
tions and about any physical, psychological and
hemorrhagic events. Adherence to treatment was
measured by counting pills.

Statistical analysis
We calculated sample size for the Current and
Past Psychological Scale fatigue score. Using
clinical recommendations, the study was to
detect a minimum treatment effect of one point
between treatment group and placebo.12 Using
effect size from a previous study,7 we therefore
powered our study to significantly detect a
decrease by 1.8 points in the treatment group
versus 0.8 in the placebo group (SD 2.0). With a
power set at 0.9 and a significance level set at
0.05, 85 patients were required in each group.
We increased the sample size by 30% to com-
penstate for drop-outs and incomplete question-
naires; therefore, the total number to be random-
ized was 240.

We used intention-to-treat analysis for all
analyses. No interim analysis or stopping rule
was judged to be necessary. To account for miss-
ing data, we used a hot-deck method with 10
imputations randomly selecting data within each
group. We compared changes in outcomes
between baseline and 12 weeks follow-up and
between placebo and iron (ferrous sulfate, FeSO₄) groups using generalized estimating equations to calculate an averaged least-squares mean between groups after adjustment for baseline values and clustering effects between physicians. We also tested whether the effects were dependent on initial hemoglobin, ferritin or transferrin saturation values. Stratified analysis for ferritin was per-protocol; we amended the analysis for hemoglobin before starting the analysis but after the data were collected. The analysis for transferrin saturation was post-hoc.

Results

Patients were recruited from Apr. 1, 2006, to Aug. 31, 2006, from 44 general practices in France. In total, 243 patients were screened for eligibility. Of these, 30 were not eligible and 15 refused to be included (Figure 1). We randomly assigned 198 patients to receive either an iron supplement (n = 102) or placebo (n = 96). Randomization ensured that the groups had similar characteristics at baseline for all outcomes. However, more patients in the iron group had a hemoglobin blood concentration of less than 13.0 g/dL and a ferritin level of less than 15 µg/L (Table 1).

Effects on outcomes

Intention-to-treat analysis showed that patients receiving the iron supplement had a 3.5 point improvement (95% confidence interval [CI] 0.3 to 6.7) in their fatigue score on the Current and Past Psychological Scale compared with those in the placebo group; thus, patients who received iron reported a 47.7% decrease in fatigue,
whereas patients in the placebo group reported a decrease of 28.8%. Iron also had significant effects on the global fatigue index from the Multidimensional Assessment of Fatigue Scale ($p = 0.03$) and its severity index ($p = 0.03$). Iron supplementation did not have any effect on anxiety or depression scores (Table 2). There were no significant effects on the indicators of quality of life. After six weeks of iron treatment, there were significant effects on hemoglobin (0.3 g/dL; $p = 0.001$), ferritin (6.8 µg/L; $p < 0.001$), mean corpuscular volume (1.2 fL; $p = 0.01$), hematocrit (0.8%; $p = 0.03$), soluble transferrin receptor (−0.4 mg/L; $p < 0.001$) and transferrin saturation (6.6%; $p < 0.001$). The results were similar after 12 weeks of treatment (Table 2; Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110950/-/DC1).

### Table 1: Baseline characteristics of trial participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Iron* n = 102</th>
<th>Placebo n = 96</th>
<th>Relative difference from placebo, † %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>36.4 ± 9.3</td>
<td>37.3 ± 9.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Previous iron deficiency</td>
<td>60 (58.8)</td>
<td>51 (53.1)</td>
<td>-9.7</td>
</tr>
<tr>
<td>Previous pregnancy</td>
<td>58 (56.9)</td>
<td>54 (56.3)</td>
<td>-10.5</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>46 (45.1)</td>
<td>37 (38.5)</td>
<td>-14.6</td>
</tr>
<tr>
<td>Depression (CAPPS score)†</td>
<td>12.1 ± 9.7</td>
<td>10.0 ± 12.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Anxiety (CAPPS score)†</td>
<td>11.4 ± 8.7</td>
<td>9.9 ± 13.0</td>
<td>13.4</td>
</tr>
<tr>
<td>Blood characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid stimulating hormone, uU/ml</td>
<td>1.72 ± 1.0</td>
<td>1.84 ± 1.1</td>
<td>6.8</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>2.86 ± 5.5</td>
<td>2.13 ± 3.3</td>
<td>-27.6§</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.5 ± 0.9</td>
<td>13.6 ± 0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Hemoglobin &lt; 13.0 g/dL</td>
<td>32 (31.4)</td>
<td>17 (17.7)</td>
<td>-43.6§</td>
</tr>
<tr>
<td>Ferritin, µg/L</td>
<td>22.5 ± 12.7</td>
<td>23.3 ± 11.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Ferritin &lt; 15 µg/L</td>
<td>33 (32.4)</td>
<td>23 (24.0)</td>
<td>-37.3§</td>
</tr>
<tr>
<td>Red blood cells, × 10^12/L</td>
<td>4.47 ± 0.31</td>
<td>4.50 ± 0.31</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean corpuscular volume, fL</td>
<td>92.0 ± 5.0</td>
<td>92.6 ± 5.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41.0 ± 2.7</td>
<td>41.6 ± 2.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Transferrin, g/L</td>
<td>2.67 ± 0.49</td>
<td>2.63 ± 0.51</td>
<td>-1.5</td>
</tr>
<tr>
<td>Soluble transferrin receptor, mg/L</td>
<td>3.44 ± 1.1</td>
<td>3.60 ± 1.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Transferrin saturation, %</td>
<td>12.6 ± 25.3</td>
<td>12.5 ± 24.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Transferrin saturation ≤ 20%</td>
<td>38 (37.3)</td>
<td>41 (42.7)</td>
<td>14.7</td>
</tr>
<tr>
<td>Fatigue, †</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPPS score for fatigue</td>
<td>25.4 ± 8.6</td>
<td>25.0 ± 8.7</td>
<td>-1.5</td>
</tr>
<tr>
<td>Global fatigue index, MAF</td>
<td>37.4 ± 6.2</td>
<td>37.0 ± 5.9</td>
<td>-0.8</td>
</tr>
<tr>
<td>Severity of fatigue, MAF</td>
<td>7.98 ± 0.95</td>
<td>7.94 ± 0.84</td>
<td>-0.4</td>
</tr>
<tr>
<td>Vitality score, SF-12</td>
<td>4.75 ± 0.96</td>
<td>4.56 ± 1.0</td>
<td>-4.2</td>
</tr>
<tr>
<td>Quality of life‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPPS score</td>
<td>48.3 ± 22.0</td>
<td>50.7 ± 21.1</td>
<td>4.7</td>
</tr>
<tr>
<td>SF-12</td>
<td>76.7 ± 12.0</td>
<td>76.2 ± 12.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>Mental score SF-12</td>
<td>34.3 ± 6.6</td>
<td>33.8 ± 6.3</td>
<td>-1.5</td>
</tr>
<tr>
<td>Physical score SF-12</td>
<td>42.5 ± 8.3</td>
<td>42.4 ± 7.6</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

Note: CAPPS = Current and Past Psychological Scale, MAF = Multidimensional Assessment of Fatigue Scale, SD = standard deviation, SF12 = short-form Self-Reported Health Questionnaire.
*Iron = prolonged-release ferrous sulfate.
†Calculated as (placebo – iron)/(iron (FeSO₄)).
‡Imputed missing data: CAPPS total: 5 in iron group, 4 in placebo group; CAPPS fatigue: 3 in iron group, 1 in placebo; CAPPS depression: 4 in iron group, 2 in placebo group; CAPPS anxiety: 2 in iron group, 4 in placebo group; MAF global fatigue index: 8 in iron group, 6 in placebo group; MAF severity index: 1 in iron group; SF-12: 2 in iron group; SF-12:* 1 in iron group.
§Considered to be a baseline imbalance.
Adjustment for baseline imbalances between the groups (C-reactive protein level, hemoglobin < 13.0 g/dL, ferritin < 15 µg/L) did not alter the results. The effects of iron on fatigue, quality of life and hemoglobin were independent of ferritin concentrations below or above 15 µg/L and of transferrin saturation below or above 20% (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.110950/-/DC1). The effects of iron supplementation on hemoglobin values were more substantial (1.0 g/dL v. 0.1 g/dL; \( p < 0.001 \)) for women whose initial hemoglobin concentration was below 13.0 g/dL. For the other biological markers (except soluble transferrin receptor concentration), there was no significant treatment benefit for patients with an initial hemoglobin value below 13 g/dL, compared with other patients (Table 3).

After adjustment for clustering at the physician level, per-protocol analysis that excluded patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean change (adjusted)* (SD)</th>
<th>Treatment effect,† mean change (adjusted), (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue score (CAPPS; 0–40 points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on score</td>
<td>−12.2 (10.2)</td>
<td>−8.7 (11.7)</td>
</tr>
<tr>
<td>Change over time, %</td>
<td>−47.7 (35.6)</td>
<td>−28.8 (57.1)</td>
</tr>
<tr>
<td>Global fatigue index (MAF; 0–50 points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on score</td>
<td>−16.2 (11.8)</td>
<td>−11.2 (10.8)</td>
</tr>
<tr>
<td>Change over time, %</td>
<td>−41.3 (30.5)</td>
<td>−30.8 (27.6)</td>
</tr>
<tr>
<td>Severity index of fatigue (MAF; 0–10 points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on score</td>
<td>−3.6 (2.5)</td>
<td>−2.7 (2.3)</td>
</tr>
<tr>
<td>Change over time, %</td>
<td>−43.3 (30.1)</td>
<td>−33.6 (27.5)</td>
</tr>
<tr>
<td>Blood characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>0.28 (0.79)</td>
<td>−0.05 (0.83)</td>
</tr>
<tr>
<td>Ferritin, µg/L</td>
<td>11.6 (13.7)</td>
<td>0.2 (11.0)</td>
</tr>
<tr>
<td>Red blood cells, ( \times 10^{12}/L )</td>
<td>0.01 (0.19)</td>
<td>−0.02 (0.21)</td>
</tr>
<tr>
<td>Mean corpuscular volume, fl</td>
<td>1.4 (3.5)</td>
<td>−0.6 (3.2)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>0.7 (2.7)</td>
<td>−0.4 (2.5)</td>
</tr>
<tr>
<td>Transferrin, g/L</td>
<td>−0.17 (0.49)</td>
<td>0.02 (0.38)</td>
</tr>
<tr>
<td>Soluble transferrin receptor, mg/L</td>
<td>−0.66 (0.69)</td>
<td>−0.13 (0.51)</td>
</tr>
<tr>
<td>Transferrin saturation, %</td>
<td>2.8 (14.2)</td>
<td>−0.9 (14.1)</td>
</tr>
<tr>
<td>Mental disorders (CAPPS; 0–40 points)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>−5.0 (6.5)</td>
<td>−4.9 (7.4)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>−5.5 (9.0)</td>
<td>−3.5 (9.1)</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF–12 (0–100 points)</td>
<td>8.8 (13.4)</td>
<td>6.0 (12.9)</td>
</tr>
<tr>
<td>Physical score, SF–12 (0–50 points)</td>
<td>5.4 (8.4)</td>
<td>3.1 (6.8)</td>
</tr>
<tr>
<td>Mental score, SF–12 (0–50 points)</td>
<td>3.5 (8.6)</td>
<td>2.7 (8.4)</td>
</tr>
<tr>
<td>CAPPS total score, (0–120 points)</td>
<td>−21.3 (20.5)</td>
<td>−16.9 (21.4)</td>
</tr>
</tbody>
</table>

Note: CAPPS = Current and Past Psychological Scale, CI = confidence interval, MAF = multidimensional assessment of fatigue scale, SD = standard deviation, SF-12 = short form Self-Reported Health Questionnaire.
*Mean differences between baseline and 12 weeks were adjusted for clustering effects at the physician level.
†Iron = prolonged-release ferrous sulfate (FeSO₄).
‡Generalized estimating equations were used to calculate the average least-squares mean between groups adjusted for baseline values and the clustering effect between physicians. A hot-deck method with 10 imputations was used to account for data that were missing and lost to follow-up.
with protocol deviations showed similar results, with a 2.1 point greater decrease in fatigue score (95% CI –2.6 to 6.7) in the iron group (n = 55) on the Current and Past Psychological Scale compared with the placebo group (n = 66).

**Adverse events**

During the study, 59/198 patients (29.8%) reported at least one adverse event: 35/102 (34.3%) in the iron group and 24/96 (25.0%) in the placebo group ($\chi^2 = 2.1$, $p = 0.2$). Twelve (11.8%) patients in the iron group and 10 (10.4%) in the placebo group reported gastrointestinal disorders. In total, five patients experienced a serious adverse event. In the iron group, one patient was admitted to hospital for abdominoplasty and another was pregnant; both interrupted their treatment but were followed-up at 12 weeks. In the placebo group, two patients were admitted to hospital, one for thyroid adenoma and one for gynecological surgery; both were lost to follow-up. A third patient was in a severe road accident. No deaths were reported, and none of the serious adverse events appeared to be related to the study treatment.

**Interpretation**

We found that iron supplementation for 12 weeks decreased fatigue by almost 50% from baseline, a significant difference of 19% compared with placebo, in menstruating iron-deficient nonanemic women with unexplained fatigue and ferritin levels below 50 µg/L. Iron supplementation did not have a significant effect on measured indicators of quality of life apart from those directly related to fatigue. However, our results suggest that iron supplementation improves hemoglobin, ferritin, hematocrit, mean corpuscular volume and soluble transferrin as early as six weeks after starting treatment.

Our study confirms and adds to the findings of the randomized placebo-controlled clinical trial of oral iron supplementation by Verdon and colleagues. They used a shorter duration (one month) and did not limit inclusion to severe fatigue; nevertheless, the effect size was similar to that in our study, except for hemoglobin, which was not measured after treatment. In addition, Krayenbuehl and coauthors found significant effects on fatigue following intravenous iron therapy and reported a similar effect, although not significant, on hemoglobin. The effects of iron on hemoglobin concentration seem to be similar to those observed in postpartum nonanemic women, military women with iron deficiency and nonanemic women following blood donation. These changes apparently occur within six weeks of starting treatment.

Patterson and colleagues’ observational findings suggested that iron could improve quality of life. However, the effect size for quality of life appears to be smaller than for fatigue alone; thus, our study was underpowered to reveal a significant effect. Positive effects on physical and psychological performances can be explained by the known effects of iron, which include improving aerobic adaptation, endurance capacity, muscle fatigability, restless leg syndrome, memory, verbal learning and cognitive function. The effects of iron deficiency on fatigue can be explained by decreased activity of iron-dependent enzymes; for example, those affecting the metabolism of neurotransmitters that enhance neurophysiologic changes. However, we presume that such physiologic changes could be confused with depression or anxiety; thus, the effect of iron supplementation on mood disor-

<table>
<thead>
<tr>
<th>Table 3: Effects of iron supplementation at 12 weeks on biological markers, by initial concentration of hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
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<tr>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
</tr>
<tr>
<td>Ferritin, µg/L</td>
</tr>
<tr>
<td>Mean corpuscular volume, fL</td>
</tr>
<tr>
<td>Hematocrit, %</td>
</tr>
<tr>
<td>Transferrin, g/L</td>
</tr>
<tr>
<td>Soluble transferrin receptor, mg/L</td>
</tr>
<tr>
<td>Transferrin saturation, %</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval.
*A hot-deck method with 10 imputations was used to account for data that were missing and lost to follow-up.*
ders remains unknown. Our results suggest that an increase in erythropoiesis could be limited to women with a hemoglobin concentration below 13.0 g/dL. The appropriateness of the official definition of the lower limit for normal hemoglobin concentrations in women has been debated. The biological definition of iron-deficiency anemia is based on the reduction of erythropoiesis due to a lack of available iron. Hemoglobin cutoff values serve as a surrogate and do not truly reflect all individuals’ erythropoietic function correctly. Our results confirm that some women with 12.0 g/dL or higher hemoglobin concentrations have increased erythropoiesis following iron supplementation, suggesting that they were iron deficient. Furthermore, blood markers do not necessarily reflect iron stores in other compartments. A recent study suggests that following blood donation, iron supplementation can improve erythropoiesis without affecting fatigue or muscular function. Therefore, fatigue might only occur once iron deficiency becomes present in brain tissue. For women with unexplained prolonged fatigue, iron deficiency should be considered when ferritin values are below 50 µg/L, even when hemoglobin values are above 12.0 g/dL. Biological markers can be tested at six weeks to confirm iron deficiency. Recent advances in neuroscience and imagery enable iron load to be observed in the central nervous system, which should make it possible to investigate brain iron deficiency independently of iron-deficiency anemia.

**Strength and limitations**

Collecting data from a network of general practitioners in private practices provided insight into the feasibility and practical implications of iron supplementation in primary care.

A major limitation of our study was that blinding could not be totally assured because of the side effects of iron supplementation that could differentiate it from a placebo, including stool colour and digestive effects. However, we did not observe any differences in constipation, stomach ache, diarrhea or other digestive events between groups because a low dose of prolonged-release ferrous sulfate was used. We did not ask participants to guess their group assignment because Bruner and colleagues found no differences between iron and placebo groups when the participants guessed about treatment assignment, despite the use of elemental iron doses that were three times higher than those used in our study. The heterogeneity of responses to treatment for both subjective and objective outcomes makes it very difficult to determine subgroups of responders. Furthermore, imputation methods require data to be missing at random, which we cannot totally assume. Another weakness of our study is that fatigue is a subjective, patient-centred measure; however, using three different measures of fatigue and confirming the results with laboratory surrogates (hemoglobin and ferritin concentrations) increased the internal validity of our results.

**Conclusion**

Iron deficiency may be an under-recognized cause of fatigue in women of child-bearing age. If fatigue is not due to secondary causes, the identification of iron deficiency as a potential cause may prevent inappropriate attribution of symptoms to putative emotional causes or life stressors, thereby reducing the unnecessary use of health care resources, including inappropriate pharmacologic treatments.

**References**


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Contributors: Pierre-Louis Druais conceived the design of the study in collaboration with Pierre Fabre Médicament. Bernard Favrat and Paul Vaucher planned the analysis; reconstructed the entire database for analysis from crude data; verified and crosschecked all data for adverse events, loss to follow-up and deviations from protocol; analyzed results, interpreted data and wrote the manuscript. Sophie Waldvogel interpreted data. All authors revised the manuscript and approved the final version submitted for publication.

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