



¹ Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

² Medication Information, Quality, and Safety (MedIQS), Pharmacy Department, Sunnybrook HSC, Toronto, Ontario, Canada

³ Division of Geriatric Psychiatry, Department of Psychiatry and Behavioural Neurosciences, Michael G. DeGroot School of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

Correspondence to M Sergeant
sergean@hhsc.ca

This article is part of a series that offers practical actions clinicians can take to support reaching net zero. Browse all the articles at <https://sandpit.bmj.com/graphics/2023/tangibleActions-v8/>. To pitch your idea for an article go to <https://bit.ly/46Et9i>

Cite this as: *BMJ* 2023;383:e075741

<http://dx.doi.org/10.1136/bmj-2023-075741>

Published: 6 November 2023

SUSTAINABLE PRACTICE

Sustainable practice: Sustainable prescribing of iron replacement therapy

Myles Sergeant,¹ Jennifer Do,² Ana Hategan³

What you need to know

- When oral iron is indicated for iron deficiency and iron deficiency anaemia, consider prescribing one pill either daily or on alternate days instead of multiple pills daily
- Consider dietary and drug interactions, eg, proton pump inhibitors, as a cause of iron deficiency; optimising iron absorption per pill can lead to a reduction in dosing as well as the associated carbon footprint of medications
- Avoid checking ferritin levels if there is no clear indication

Treatment of iron deficiency (with or without anaemia) is an area where clinicians can implement updated recommendations on dose and frequency of iron supplementation that can have a clinical benefit for patients and also help mitigate environmental harms from healthcare practices.

Why change is needed

Production and use of medications represent 12–25% of the greenhouse gas emissions from healthcare, the largest item in the supply chain with respect to carbon footprint.^{1,2} An accessible entry point for clinicians to reduce their environmental impact is to focus on optimising prescribing.

Iron deficiency is a continuum that starts with iron depletion from the body's stores, which can progress to anaemia. Iron deficiency affects an estimated 2 billion people and is one of the leading risk factors for disability and death worldwide.³ The British Society of Gastroenterology recently updated its guidelines for management of iron deficiency anaemia.⁴ Recommendations now include dosing iron once daily or on alternate days instead of two to three times daily.⁴ These changes provide an opportunity for clinicians to reassess how they prescribe iron supplements and to include environmental considerations in their thought process. Few systematic analyses are available that consider the environmental impact of the medication life cycle, but clinicians can treat patients and reduce their carbon footprint by prescribing fewer medications along with ordering fewer tests, where feasible.⁵

Evidence for the solution

Strategies for correcting iron deficiency include dietary changes and iron supplementation.³ Here we focus on the management options for when oral iron supplementation is indicated. Oral iron salts are the standard treatment options as they are inexpensive,

effective, safe, and readily available,⁴ however they can be poorly tolerated (eg, typically because of gastrointestinal symptoms) leading to poor adherence to treatment.⁶ Finding a format and dose that patients will more likely adhere to can help reduce drug waste and therefore environmental impact.

Previous recommendations for treating iron deficiency suggested taking iron in divided doses throughout the day,⁶ on the basis that iron absorption from oral iron supplements is low. However, recent studies which look at the impact of dosing regimens on hepcidin levels and iron absorption have led to recommendations to dose iron supplements daily or on alternate days.⁷ Hepcidin is a marker of iron metabolism, with hepcidin levels following a diurnal pattern and increasing after oral iron intake, impairing fractional absorption of subsequent doses.⁴ One crossover study in 19 women with iron deficiency anaemia who received 100 mg or 200 mg iron as ferrous sulfate found that alternate day dosing resulted in higher fractional iron absorption, with a trend to lower incidences of gastrointestinal side effects compared with daily dosing.⁷ Two open-label randomised controlled trials compared iron absorption from iron supplements given on consecutive days versus alternate days and given as a single dose versus twice daily split dosing, in women with depleted iron stores.⁸ The main findings were that alternate day dosing of 60 mg elemental iron significantly increased fractional and total iron absorption compared with daily dosing, and fractional and total absorption were not increased by splitting a dose of 120 mg iron to 60 mg twice daily.⁸ Another randomised controlled trial of 62 patients with iron deficiency anaemia compared 120 mg elemental iron on alternate days with 60 mg elemental iron twice daily.⁹ This trial found that iron twice daily produced a faster rate of haemoglobin rise, however, similar rises were seen with alternate day dosing after the same total dose had been given, along with a lower prevalence of nausea. Patients with very severe anaemia (haemoglobin <6 g/dL), as well as certain comorbidities, were excluded from this study. A large randomised controlled trial of 200 patients with iron deficiency anaemia found similar efficacy in the clinically meaningful increase in haemoglobin between 60 mg elemental iron as a single dose on consecutive days versus 120 mg on alternate days after eight weeks.¹⁰ This study did not measure hepcidin levels or inflammatory markers which could have affected ferritin levels.¹⁰ These studies highlight that alternate day dosing appears to produce at least similar results in clinically meaningful increases in haemoglobin levels

compared with consecutive days (single daily or twice daily doses) of oral iron.^{7 9 10} Although it may take longer to treat the iron deficiency,^{7 9} the increased absorption per pill could result not only in fewer side effects but also a reduction in the carbon footprint of these medications. The most recent updated guidelines of the British Society of Gastroenterology reflect this evidence as well, with the recommendation that elemental iron can be given at doses between 50 and 150 mg daily on consecutive days or on alternate days for patients with iron deficiency and associated anaemia.⁴

What you can do

Depletion of iron stores may result from decreased intake (eg, limited diet), increased demand (eg, menstruation, cancer), and impaired absorption (eg, gastric or bariatric surgery).³ After diagnosing the

condition, management includes treating the underlying cause and starting iron supplementation and dietary counselling.^{6 11}

Table 1 outlines several steps that clinicians may consider in sustainable prescribing for treatment of iron deficiency with or without anaemia, when the correct diagnosis has been made (which is beyond the scope of this article), the underlying causes for iron store depletion have been addressed, and the patient requires iron supplementation.^{6 7 9 11-17} Clinicians may consider prescribing one tablet of 100-150 mg elemental iron on alternate days instead of a 60 mg elemental iron tablet daily or twice daily to offer a comparable clinical benefit, reduce side effects, and reduce the associated carbon footprint of each tablet from manufacturing, tableting, packaging, distribution, and waste.

Table 1 | Steps for clinicians to ensure sustainable prescribing for iron replacement therapy: WASTED-RX^{6 7 9 11-17}

Issues to address	Comments
What matters to the patient?	Consider implementing “What matters to you” for person centred care in place of “What’s the matter with you?” ¹² For example, patients may wish to improve symptoms of iron deficiency, have a lower pill burden, or fewer medication side effects
Affordability and adherence	Can your patient afford a proper diet or medication? Consider “social prescribing” by referring your patient to local, non-clinical services that are chosen according to the patient’s needs and goals of care (eg, https://www.who.int/publications/i/item/978929061976512)
Supplement selection	Multiple oral iron supplements are available (ie, ferrous salts, iron complexes) that are low cost and safe. ⁶ Traditionally iron supplements were dosed one to three times daily. Recent small studies, however, show that single doses on alternate days can help optimise iron absorption. ^{7 9} Phone apps are available to remind patients about timing
Tolerability	Iron absorption is enhanced when supplements are taken on an empty stomach. If tolerance issues occur, consider adjusting the regimen (eg, using a format with less elemental iron, taken less frequently) If necessary, supplements can be taken with meals ^{6 7 9}
Education for patient	To help prevent iron deficiency, encourage all patients to consume a diet with sufficient iron. Plant based sources that are rich in non-heme iron include cooked soybeans, tofu, and lentils. Take iron supplement 30-60 minutes before eating, including tea, coffee, and dairy products. ^{13 15} Consider a dietician referral as indicated
Drug interactions	Drug interactions can affect iron levels (eg, calcium tablets have a short term effect on iron absorption. ¹³) Discontinue or separate timing when possible. Review drug interactions with a pharmacist if available. Recent evidence indicates that vitamin C as an adjunct does not increase tolerability or absorption from iron supplements ¹⁶
Reassessment	Every laboratory test comes with an associated carbon footprint. Avoid checking ferritin levels if there is no clear indication to do so. When iron supplementation is required, it may take up to six months to replenish iron stores. Reassess the need for iron supplementation with clinical assessment and periodic laboratory testing. Further investigations are needed if iron deficiency has not been corrected ¹¹
Expiry date of medications	A future direction of research would be to consider the effectiveness of medications taken past their expiry dates. ¹⁷ The effectiveness of iron supplements past the expiry date is unknown

Aside from dosage, other factors need to be considered in the sustainable prescribing of iron replacement therapy. Non-adherence to medications is common.¹⁸ An investigation of the effects of cost related non-adherence on patient outcomes in the US found that affordability is the most common reason for non-adherence with medications, making social determinants of health an important part of management.¹⁹ Social prescribing services can give patients access to interventions to address social needs, such as financial support, community connection, and education on good nutrition.¹² This may include referral to an income clinic or exploring local food access options to find treatment in a non-medical context, as opposed to receiving a prescription for iron supplementation.

Consider the impact of drug interactions. Prolonged use of medications that reduce gastric acid levels, such as proton pump inhibitors, can lead to iron deficiency.²⁰ Calcium can have a short

term effect on iron absorption and should be taken at a different time of day.¹³ Coffee and tea contain various polyphenols that may have an affinity for iron and impact its absorption, leading to iron deficiency when consumed in large quantities.^{14 15} Generally, the best time to take an iron supplement is between meals or 30-60 minutes before eating, including tea, coffee, and dairy products.¹³⁻¹⁵

Vitamin C supplementation, which has been routinely used with oral iron supplements, is found to be less beneficial than previously reported for improving iron absorption and haemoglobin recovery.¹⁶ This challenges the need for patients to take vitamin C along with their iron supplement, and could reduce their pill burden.

Education into practice

- How might you establish whether dietary or socioeconomic factors are contributors in a patient with iron deficiency?

- What changes at a practice or system level could you make to encourage clinicians to implement the actions in this article? How would you measure the effect of these?

Patient involvement: no patients were directly involved in the creation of this article.

Contributorship and the guarantor: MS conceived the article and is guarantor. All authors wrote and reviewed the article, and created the table.

Competing interests: Myles Sergeant is the executive director of the Canadian Coalition for Green Healthcare. The authors are members of PEACH Health Ontario (Partnerships for Environmental Action by Clinicians and Communities for Hospitals/Healthcare Facilities).

Provenance and peer review: commissioned; externally peer reviewed.

The authors thank Harjas Kaur, Master of Engineering and Public Policy at McMaster University, for her research on the manufacture of iron salts.

- 1 Braithwaite J, Pichumani A, Crowley P. Tackling climate change: the pivotal role of clinicians. *BMJ* 2023;382:e076963. doi: 10.1136/bmj-2023-076963 pmid: 37770093
- 2 Eckelman MJ, Sherman JD, MacNeill AJ. Life cycle environmental emissions and health damages from the Canadian healthcare system: an economic-environmental-epidemiological analysis. *PLoS Med* 2018;15:e1002623. doi: 10.1371/journal.pmed.1002623 pmid: 30063712
- 3 Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007;370:-20. doi: 10.1016/S0140-6736(07)61235-5 pmid: 17693180
- 4 Snook J, Bhalal N, Beales ILP, et al. British Society of Gastroenterology guidelines for the management of iron deficiency anaemia in adults. *Gut* 2021;70:-51. doi: 10.1136/gutjnl-2021-325210 pmid: 34497146
- 5 Drew J, Rizan C. *HealthcareLCA Database*. HealthcareLCA, 2022. healthcarelca.com/database
- 6 Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. *Am J Clin Nutr* 2015;102:-94. doi: 10.3945/ajcn.114.103366 pmid: 26561626
- 7 Stoffel NU, Zeder C, Brittenham GM, Moretti D, Zimmermann MB. Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women. *Haematologica* 2020;105:-9. doi: 10.3324/haematol.2019.220830 pmid: 31413088
- 8 Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *Lancet Haematol* 2017;4:-33. doi: 10.1016/S2352-3026(17)30182-5 pmid: 29032957
- 9 Kaundal R, Bhatia P, Jain A, et al. Randomized controlled trial of twice-daily versus alternate-day oral iron therapy in the treatment of iron-deficiency anemia. *Ann Hematol* 2020;99:-63. doi: 10.1007/s00277-019-03871-z pmid: 31811360
- 10 Pasupathy E, Kandasamy R, Thomas K, Basheer A. Alternate day versus daily oral iron for treatment of iron deficiency anemia: a randomized controlled trial. *Sci Rep* 2023;13. doi: 10.1038/s41598-023-29034-9 pmid: 36725875
- 11 Balendran S, Forsyth C. Non-anaemic iron deficiency. *Aust Prescr* 2021;44:-6. doi: 10.18773/austprescr.2021.052 pmid: 35002031
- 12 World Health Organization. A toolkit on how to implement social prescribing. <https://www.who.int/publications/i/item/9789290619765>
- 13 Lönnerdal B. Calcium and iron absorption-mechanisms and public health relevance. *Int J Vitam Nutr Res* 2010;80:-9. doi: 10.1024/0300-9831/a000036 pmid: 21462112
- 14 Fan FS. Iron deficiency anemia due to excessive green tea drinking. *Clin Case Rep* 2016;4:-6. doi: 10.1002/ccr3.707 pmid: 27830072
- 15 Lee J. Association between coffee and green tea consumption and iron deficiency anemia in Korea. *Korean J Fam Med* 2023;44:-70. doi: 10.4082/kjfm.44.2E pmid: 36966735
- 16 Li N, Zhao G, Wu W, et al. The efficacy and safety of vitamin C for iron supplementation in adult patients with iron deficiency anemia: a randomized clinical trial. *JAMA Netw Open* 2020;3:e2023644. doi: 10.1001/jamanetworkopen.2020.23644 pmid: 33136134
- 17 Zilker M, Sörgel F, Holzgrabe U. A systematic review of the stability of finished pharmaceutical products and drug substances beyond their labeled expiry dates. *J Pharm Biomed Anal* 2019;166:-35. doi: 10.1016/j.jpba.2019.01.016 pmid: 30660807
- 18 Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014;2014:CD000011. doi: 10.1002/14651858.CD000011.pub4 pmid: 25412402
- 19 Van Alsten SC, Harris JK. Cost-related nonadherence and mortality in patients with chronic disease: a multiyear investigation, National Health Interview Survey, 2000-2014. *Prev Chronic Dis* 2020;17:E151.20.
- 20 Tran-Duy A, Connell NJ, Vanmolkot FH, et al. Use of proton pump inhibitors and risk of iron deficiency: a population-based case-control study. *J Intern Med* 2019;285:-14. doi: 10.1111/joim.12826 pmid: 30141278