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EFFICACY AND TOLERABILITY OF DIFFERENT ORAL IRON PREPARATIONS IN IRON DEFICIENCY ANEMIA: REVIEW

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ABSTRACT

Background: iron deficiency anemia (IDA) is a widespread, preventable condition that diminishes work capacity, cognition, and overall health. Dysregulation of iron homeostasis — principally via hepcidin-mediated sequestration — distinguishes absolute deficiency from functional deficiency, guides diagnostic interpretation and helps to choose the type therapy.
Aim: The aim of this article is to compare the available oral iron supplements with respect to efficacy, tolerability and practical use. It summarizes current evidence regarding optimal dosing and frequency of administration in individuals with iron deficiency and iron-deficiency anemia.
Methods: narrative review of literature up to 2025, prioritizing recent meta-analyses, systematic reviews, randomized controlled trials, phase III randomized studies and other high-quality studies. Searches were conducted in PubMed/MEDLINE, Embase, Web of Science and Google Scholar. Key search terms included oral iron, ferrous sulfate, liposomal iron, sucrosomial iron, ferric maltol and ferrous bisglycinate. This review compares their efficacy and tolerability. Study selection, data extraction, and quality evaluation followed standard review procedures; findings were synthesized and summarized in tables.
Results: new supplements generally achieve comparable or faster hematologic responses at lower elemental iron doses and are associated with fewer gastrointestinal side effects, which may improve adherence, particularly in patients intolerant of ferrous salts or with inflammatory conditions. Dosing approaches that account for hepcidin dynamics (alternate-day or single morning dosing) enhance absorption. Heterogeneity in study populations, dosing regimens and outcome measures limits direct comparisons.
Conclusion: oral iron formulations show broadly similar efficacy; selection should prioritize tolerability, comorbidity context, and dosing strategies that optimize absorption. Individualized therapy with routine monitoring of hemoglobin and ferritin improves outcomes and adherence.

KEYWORDS

Iron Deficiency, Anemia, Oral Iron, Iron Supplementation, Side Effects, Treatment

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Introduction

Iron-deficiency anemia (IDA) remains a major global public health problem, affecting roughly one quarter of the world's population — about two billion people — particularly in low- and middle-income countries where inadequate dietary iron and parasitic blood loss are common contributors. (Kolarš et al., 2025; Pasricha et al., 2021; McLean et al., 2009)

Although the epidemiology varies by setting, the clinical and public-health consequences — reduced work capacity, impaired cognition, and adverse maternal-child outcomes — point to an urgent need for improved detection and care.

At the biological level, systemic iron balance is tightly regulated. Hepcidin, a hepatic peptide hormone, is the principal mediator that limits iron export from enterocytes and macrophages and thereby determines plasma iron availability. (McLean et al., 2009)

This mechanism explains the distinction between absolute iron deficiency (depleted stores) and functional iron deficiency (adequate stores but restricted availability during inflammation), a distinction that has direct implications for laboratory interpretation and therapeutic choice. (McLean et al., 2009)

The most frequent causes of IDA are chronic blood loss (most often gastrointestinal or menstrual), inadequate dietary intake or poor iron bioavailability, and impaired absorption or inflammation-driven sequestration; these mechanisms commonly coexist in the same patient. Typical clinical features include fatigue, reduced exercise tolerance, pallor, occasional tachycardia, and signs of tissue iron deprivation such as

mucocutaneous changes, restless legs, paresthesias, and atrophic glossitis; symptom severity may be muted when anemia develops slowly, so objective laboratory confirmation is essential.

Dietary iron is absorbed mainly in the duodenum as heme and non-heme iron; hepcidin controls iron export from enterocytes and macrophages, so elevated hepcidin during inflammation reduces plasma iron availability and can produce functional iron deficiency despite normal or increased ferritin. (Williams et al., 2023; Kumar et al., 2022; Camaschella et al., 2015; McLean et al., 2009)

Table 1. Diagnostic criteria for iron deficiency anemia (Kumar et al., 2022)

Serum markers	Diagnosis for iron
Hemoglobin	< 13,0 g/dl for males < 12,0 g/dl for females < 11,0 g/dl in pregnancy
Mean corpuscular volume (MCV)	Low
Iron	Reduced
Ferritin*	< 30 µg/L if no inflammation < 100 µg/L if inflammation
Transferrin**	Raised
Total iron binding capacity (TIBS)	Raised
Transferrin saturations	< 20%

* Is a positive acute phase protein and can be raised in inflammatory conditions.

** Is a negative acute phase protein and can be normal or reduced in inflammatory conditions.

Clinically, IDA arises from three principal pathways noted above, and these should guide both investigation (for example, evaluation for sources of blood loss) and treatment choice (oral versus intravenous iron, consideration of inflammation and hepcidin status). Objective laboratory confirmation using the criteria in Table 1 helps distinguish absolute iron deficiency (depleted stores) from functional iron deficiency (restricted availability during inflammation) and directs further management. (Williams et al., 2023; Kumar et al., 2022)

Aim of the publication

The aim of this article is to compare the available oral iron supplements with respect to efficacy, tolerability and practical use. It summarizes current evidence regarding optimal dosing and frequency of administration in individuals with iron deficiency and iron-deficiency anemia.

Methodology

This work was conducted as a narrative review based on meta-analyses, randomized controlled trials (RCTs), phase III randomized studies, systematic reviews, prospective cohort studies and several other investigations published up to 2025. Databases searched included PubMed/MEDLINE, Embase, Web of Science, and Google Scholar. Search terms included: “iron-deficiency anemia,” “oral iron,” “ferrous sulfate,” “ferrous fumarate,” “ferrous gluconate,” “sucrosomial iron,” “ferric maltol,” “liposomal iron,” “ferrous bisglycinate,” and “iron intolerance.” This review incorporates the most comprehensive and up-to-date studies presenting outcomes such as changes in hemoglobin concentration, ferritin levels, tolerability, and adherence in the treatment of iron-deficiency anemia. Study selection, data extraction, and quality evaluation followed standard review procedures; findings were synthesized and summarized in tables.

Results

When iron-deficiency anemia is diagnosed, an important goal is appropriate supplementation and the replenishment of iron stores in the body. Iron can be administered orally or intravenously. (Lo et al., 2023; Girelli et al., 2018) Oral iron preparations are considered the first-line treatment due to their convenience of use and relatively low cost. (Pantopoulos, 2024) Oral supplementation requires the use of 150–200 mg of elemental iron per day, administered in two or three divided doses. (Wu & Tsai, 2016) However, recent studies have shown that high doses of iron increase hepcidin levels — a sensitive marker that responds even to small rises in iron — thereby inhibiting its absorption. Only about 10–20% of the iron is absorbed, which leads to

the accumulation of unabsorbed iron in the gastrointestinal tract. This residual iron may irritate the intestines and trigger inflammation, potentially resulting in adverse effects and prompting patients to discontinue treatment on their own. (Kolars et al., 2024; Celis et al., 2023)

Other studies have also confirmed that iron absorption improves with single daily doses or with alternate-day dosing. (Stoffel et al., 2020; Melina et al., 2016) Hepcidin levels follow a circadian rhythm and typically increase throughout the day. This rise is additionally amplified by morning iron supplementation. Therefore, to maximize iron absorption, administering it in a single morning dose is considered the most optimal approach. (Kolarš et al., 2025; Stoffel et al., 2020)

Oral iron should be taken on an empty stomach, at least one hour before a meal. It has been shown that the percentage of absorbed iron is higher when taken fasting compared with iron taken with food. (Wu & Tsai, 2016) Many foods and beverages inhibit iron absorption. It has been shown that phytates found mainly in legumes, polyphenols present in coffee and tea, as well as calcium-fortified products and dairy, reduce iron absorption. A similar effect has been observed with the use of antacids and proton pump inhibitors. (Kolarš et al., 2025; Gómez-Ramírez et al., 2023; Hamano et al., 2020)

In summary, according to the studies cited, iron should be taken in the morning on an empty stomach at a dose of 40 mg of elemental iron daily or 60 mg every other day, combined with vitamin C, which enhances iron absorption. (Kolarš et al., 2025; Stoffel et al., 2020)

To assess the effectiveness of iron supplementation, the dynamics of hemoglobin increase should be monitored during the first 4 weeks. (van Santen et al., 2014) The expected increase in hemoglobin concentration is 1–2 g/dL within 2–4 weeks. (Girelli et al., 2018; Dignass et al., 2015) An increase in hemoglobin <1.0 g/dl after 2 weeks of oral iron administration may be a prognostic factor for an insufficient response to the treatment. (Kolarš et al., 2025; Okam et al., 2017) Another indicator used to monitor the effectiveness of oral iron therapy is the reticulocyte count. Reticulocytosis usually occurs 7–10 days after the start of treatment. Therapy should be continued for approximately three months after hemoglobin levels normalize in order to restore iron stores. (Kolarš et al., 2025)

There are many oral iron preparations available. Despite numerous clinical studies evaluating the efficacy of different iron formulations, no single preparation has been shown to be superior to others in replenishing iron deficiency. (Gamad et al., 2021) The following section of the review discusses iron salts as well as newer available iron formulations that can be used in the treatment of anemia.

Iron salts

The most commonly used oral preparations are iron (II) salts. Various iron salts are available, including ferrous sulfate, ferrous fumarate, and ferrous gluconate. These formulations are available in tablet and liquid forms. (Pantopoulos, 2024) Although they are inexpensive medications, they are associated with numerous adverse effects. A meta-analysis conducted by Tolkien Z et al. in 2015 showed that the most frequently reported side effects of oral iron supplementation were gastrointestinal complaints: constipation (12%), nausea (11%), and diarrhea (8%). Additionally, supplementation with ferrous sulfate significantly increased the incidence of these side effects compared with placebo and intravenous iron. (Tolkien et al., 2015) Moreover, it has been shown that higher doses of iron are more frequently associated with adverse effects such as abdominal discomfort, nausea, vomiting, changes in bowel movements, and black stools. (Lo et al., 2023) These findings were also confirmed in another meta-analysis including over 10,000 patients. It was shown that gastrointestinal adverse effects were reported in 43% of patients using ferrous fumarate, 31% of those using ferrous gluconate, and 30% of those using ferrous sulfate. (Cancelo-Hidalgo et al., 2013)

Sucrosomial iron

Sucrosomial iron is a novel oral form of iron in which iron pyrophosphate is protected by a so-called “sucrosome”, a complex composed of a bilayer phospholipid membrane and a matrix made of sucrose esters and fatty acids. (Fabiano et al., 2018; Gómez-Ramírez S et al., 2018) This structure provides resistance to the acidic environment of the stomach and allows effective absorption of iron in the form of intact nanoparticles through three pathways: via intestinal cells, paracellularly, and intracellularly. (Fabiano et al., 2018) As a result, absorption is largely independent of hepcidin. (Ciudin et al., 2018)

In 2021, Giordano G et al. conducted a multicenter randomized study comparing the efficacy of oral sucrosomial iron and intravenous sodium ferric gluconate. The results showed fairly comparable effectiveness between the two preparations. An increase in hemoglobin of 1 g/dL was achieved within 9 days of starting sucrosomial iron therapy, compared to 7 days with intravenous sodium ferric gluconate. Achieving the target

hemoglobin level of 12 g/dL took 4 weeks with sucrosomial iron and 3.5 weeks with intravenous iron. For comparison, achieving a 1 g/dL increase in hemoglobin with ferrous sulfate would require 18 days, assuming a tablet contains 65 mg of elemental iron, of which 25 mg is absorbed, and optimal administration every other day in a morning dose. Reaching the target hemoglobin of 12 g/dL with ferrous sulfate would take 72 days of treatment. (Giordano et al., 2021)

Many studies have shown a reduced risk of adverse effects during the use of sucrosomial iron. (Bastida et al., 2021; Giordano et al., 2021; Abbati et al., 2019) When sucrosomial iron was taken on an empty stomach, 16% of patients reported side effects such as abdominal pain and diarrhea. In contrast, taking sucrosomial iron with a meal reduced the incidence of adverse effects, with only 5% of patients reporting side effects. (Giordano et al., 2021)

The results of the above studies have also been confirmed in several other investigations. It has been shown that oral sucrosomial iron can be an alternative to intravenous iron administration, particularly in patients with anemia and chronic inflammatory conditions. (Bertani et al., 2021; Ciudin et al., 2018; Mafodda et al., 2017) In 2021, Bertani et al. conducted a prospective randomized study involving 40 patients with ulcerative colitis in remission. The results showed a comparable increase in hemoglobin levels with the use of oral sucrosomial iron and intravenous carboxymaltose infusion. No significant gastrointestinal adverse effects were observed in the sucrosomial iron group. (Bertani et al., 2021)

Moreover, several studies have shown that effective supplementation with sucrosomial iron requires lower doses compared to classical iron (II) salts, while achieving a greater increase in hemoglobin and ferritin levels. (Bastida et al., 2021; Elli et al., 2018)

Over 12 weeks of treatment, hemoglobin levels increased by 2.7 g/dL with sucrosomial iron (at a dose of 30–60 mg per day), whereas with ferrous sulfate (at a dose of 105–210 mg per day), the increase was 1.4 g/dL. (Bastida et al., 2021)

In 2018, Elli L et al. conducted a prospective study involving 43 patients with celiac disease. Both ferrous sulfate and sucrosomial iron (used in cases of ferrous sulfate intolerance) resulted in a comparable increase in hemoglobin levels after three months of treatment. However, the dose of sucrosomial iron was three times lower than that of ferrous sulfate. Similar to the previous study, fewer adverse effects were observed in the sucrosomial iron group. (Elli et al., 2018)

Ferric maltol

Another new oral iron preparation is ferric maltol. It consists of a stable iron complex with a sugar derivative—trimaltol. This structure allows for increased iron bioavailability. (Cancelo-Hidalgo et al., 2013) Ferric maltol facilitates the delivery of iron to enterocytes while keeping unabsorbed iron in a chelated, redox-neutral form. For iron to be absorbed, it must first dissociate from the maltol complex. Free maltol is absorbed separately, undergoes independent metabolism, and is excreted in the urine. (Kolarš et al., 2025; Pantopoulos, 2024)

Ferric maltol has been shown to be effective in the treatment of iron-deficiency anemia in patients with inflammatory bowel disease and chronic kidney disease. An average increase in hemoglobin of 2 g/dL was observed after 12–16 weeks of treatment. Ferritin levels and transferrin saturation also increased. (Schmidt et al., 2021) In another clinical study involving patients with inflammatory bowel disease, ferric maltol demonstrated comparable efficacy to intravenous iron. The mean increase in hemoglobin at 12 weeks of treatment was 2.5 g/dL for both ferric maltol and ferric carboxymaltose. Both agents were well tolerated and showed similar long-term effectiveness. (Howaldt et al., 2022)

In a phase III randomized study, Gasche C et al. found that ferric maltol has good gastrointestinal tolerability. In a study involving patients with anemia and inflammatory bowel disease, treatment discontinuation due to adverse effects was comparable to that of the placebo group, at approximately 10%. (Gasche et al., 2015) Good tolerability was also observed in long-term studies. (Pergola & Kopyt, 2021; Schmidt et al., 2016)

Liposomal iron

Liposomal iron is iron pyrophosphate encapsulated in phospholipid vesicles called liposomes. (Pisani et al., 2015) This structure, similar to that of sucrosomial iron, provides protection against the acidic environment of the stomach and enhances iron absorption through the intestinal mucosa. (Cesarano et al., 2024)

Like ferric maltol, liposomal iron has been shown to be effective in treating anemia in patients with inflammatory bowel disease and chronic kidney disease. (de Alvarenga Antunes et al., 2020; Maladkar et al.,

2020) Liposomal iron, similarly to sucrosomial iron, is also associated with fewer gastrointestinal adverse effects. (de Alvarenga Antunes et al., 2020; Biniwale et al., 2018) In randomized controlled trial, Bengelloun Zahr S et al. demonstrated that liposomal iron increased hemoglobin levels and other parameters in the treatment of anemia in patients with chronic kidney disease, although to a lesser extent compared with intravenous iron. (Bengelloun Zahr et al., 2024)

Ferrous bisglycinate

Ferrous bisglycinate is an amino acid chelate of iron, consisting of two glycine molecules bound to an iron (II) cation. This structure has been shown to be highly stable and provides twice the bioavailability compared to classical iron (II) salts. (Duque et al., 2014; Milman et al., 2014) As a result, a significant portion of supplemented iron is absorbed by enterocytes, which is associated with fewer gastrointestinal adverse effects. (Name et al., 2018)

A meta-analysis by Fischer Jordie AJ et al. primarily included children and adult populations. The study evaluated the effect of ferrous bisglycinate supplementation, compared with other iron supplements, on the dynamics of anemia markers such as hemoglobin and ferritin. It was shown that supplementation with ferrous bisglycinate in pregnant women for 4–20 weeks resulted in higher hemoglobin levels and good gastrointestinal tolerability. Ferrous bisglycinate is often administered at a lower dose of elemental iron than most other iron salts due to its higher bioavailability. (Fischer Jordie et al., 2023) Bumrungpert A et al. conducted a randomized controlled trial evaluating the efficacy of ferrous bisglycinate and folinic acid supplementation in pregnant women with iron deficiency. The results showed that increases in hemoglobin and other anemia markers were higher in the ferrous bisglycinate group than in the ferrous fumarate group. For comparison, in the ferrous bisglycinate group, baseline hemoglobin was approximately 10.04 g/dL, increasing to 12.40 g/dL after 3 months of supplementation and 12.82 g/dL after 6 months. In the ferrous fumarate group, baseline hemoglobin was 10.17 g/dL, increasing to 11.78 g/dL after 3 months and 12.09 g/dL after 6 months. Increases in other markers, such as ferritin and transferrin saturation, were also higher at each stage in the ferrous bisglycinate group. Better tolerability and fewer gastrointestinal adverse effects were observed. Compared to ferrous fumarate, lower doses of ferrous bisglycinate achieved more favorable outcomes. (Bumrungpert et al., 2022)

All relevant information regarding various oral iron preparations is presented in Table 2.

Table 2. Comparison of common oral iron supplements

Type of supplements	Amount of elemental iron, mg	Advantages	Effects
Ferrous sulfate / ferrous fumarate [7, 10, 22]	**60–100 mg**	High elemental iron; low cost	Nausea; constipation; abdominal pain
Ferrous gluconate [7]	**30–40 mg**	Often better gastrointestinal tolerability than sulfat	Mild gastrointestinal upset
Sucrosomial iron [2, 17, 29]	**30-60 mg**	Protected iron in a sucrosome; acid-resistant; hepcidin-independent uptake	Fewer GI adverse events; 16% side effects empty stomach vs 5% with food; faster Hb rise at lower doses
Ferric maltol [8, 34, 35]	**~30 mg (ferric maltol)**	Good tolerability in patients with IBD or CKD; stable iron delivery	Headache; mild gastrointestinal symptoms
Liposomal iron [2, 7, 39]	**Variable**	Iron encapsulated in liposomes; protected from gastric acid; enhanced mucosal uptake	Fewer GI side effects than ferrous salts; Hb rise something less than IV iron
Ferrous bisglycinate (chelated iron) [2, 46, 47]	**Variable (chelated dose)**	Enhanced absorption; improved gastrointestinal tolerability	Rare gastrointestinal complaints

Discussion

Based on the available data, the new oral iron supplements appear to be an optimal solution for individuals with iron deficiency and iron-deficiency anemia, especially in cases of intolerance to traditional ferrous (II) salts. The results of the studies presented in this article confirm the effective absorption and increased bioavailability of these newer forms of iron, allowing for satisfactory treatment outcomes. (Kolarš et al., 2025; Pantopoulos, 2024) Compared with classical ferrous (II) salts, a meaningful increase in hemoglobin and other anemia markers (ferritin, transferrin saturation) was observed within a shorter period and with the use of lower iron doses. (Fischer Jordie et al., 2023; Elli et al., 2018; Cancelo-Hidalgo et al., 2013) All new preparations (sucrosomial iron, ferric maltol, liposomal iron, and ferrous bisglycinate) demonstrate good gastrointestinal tolerance, which enhances the likelihood of effective treatment and patient adherence. Their improved bioavailability and stable structures enable maximal iron absorption while minimizing the risk of adverse effects. (Giordano et al.,2021; Biniwale et al., 2018; Name et al., 2018; Gasche et al., 2015) Numerous studies have shown that these new iron formulations are effective in treating iron-deficiency anemia in patients with chronic inflammation. The results confirm the therapeutic efficacy of sucrosomial iron, ferric maltol, and liposomal iron in conditions such as celiac disease, inflammatory bowel disease, and chronic kidney disease. (de Alvarenga Antunes et al., 2020; Maladkar et al., 2020; Elli et al., 2018) Their long-lasting effects have also been well documented. (Pergola & Kopyt., 2021; Schmidt et al., 2016) Multiple studies have demonstrated that sucrosomial iron and ferric maltol may serve as viable alternatives to intravenous iron. (Howaldt et al., 2022; Bertani et al., 2021; Ciudin et al., 2018; Mafodda et al., 2017) Ferrous bisglycinate, in turn, is a well-tolerated and effective option for treating iron-deficiency anemia in pregnant women and children — populations with increased iron requirements. (Fischer Jordie et al., 2023; Bumrungpert et al., 2022)

However, the studies presented in this article have certain limitations. The first is heterogeneity: each study included different patient groups in terms of sex, age, comorbidities, and chronic medications, all of which could influence iron absorption. Some studies also involved small sample sizes. Another factor was the variability in baseline hemoglobin levels and other anemia markers (ferritin, transferrin, transferrin saturation). Because ferritin is an acute-phase protein, its levels may not accurately reflect true iron stores in individuals with chronic inflammation. A third limitation concerns the different dosing regimens used for each iron formulation, which could have affected the proportion of iron absorbed. Observation periods and parameter monitoring varied across studies as well. In addition, some studies were single-arm, with the control group receiving placebo.

Despite the many benefits highlighted above, the cost of therapy with these new iron supplements remains higher than that of classical ferrous (II) salts. (Pantopoulos, 2024) Currently, there is no definitive evidence indicating the superiority of one specific preparation over another. Further research is needed to evaluate the efficacy, tolerability, and optimal dosing of different types of oral iron supplements in targeted patient populations to achieve desired therapeutic goals.

Conclusions

Oral iron therapy is the foundation of treatment for iron deficiency and IDA. Ferrous salts are effective and inexpensive, but often limited by gastrointestinal intolerance. Alternative formulations — sucrosomial iron, ferric maltol, liposomal iron and ferrous bis-glycinate — provide comparable efficacy with improved tolerability in selected populations. Dosing strategies that reflect hepcidin dynamics, particularly alternate-day regimens, enhance absorption and adherence. Aligning formulation choice and dosing strategy with patient-specific factors — including severity of deficiency, comorbidities, tolerability, and adherence history— optimizes therapeutic outcomes and helps reduce the global burden of iron deficiency.

Disclosure

Author Contributions

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