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Review

Tolerability of different oral iron supplements: a systematic review

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Abstract

Objective:
A systematic review was conducted to analyze the tolerability of several oral iron supplements based on data obtained in available publications and to report the incidence of adverse effects (AEs) for each supplement both overall and gastrointestinal.

Methods:
Electronic databases – Medline, the Cochrane Library, and Embase were searched for studies published up to January 2009. Clinical or observational studies reporting data on the tolerability of oral iron supplements were included. Results were described statistically and a quasi-binomial logistic regression model was developed to evaluate and compare the tolerability of the supplements studied.

Results:
For this review 111 studies were included, with data on 10,695 patients. Ferrous sulfate with mucoproteose had the lowest incidence of AEs (4.1% for overall AEs, 3.7% for gastrointestinal AEs [GAEs]) and was used as the reference supplement in the regression model. Incidence rates of overall AEs for the other supplements were 7.3% for iron protein succinylate [GAEs: 7%; OR for AE compared to the reference supplement, 1.96], 23.5% for ferrous glycine sulfate [GAEs: 18.5%; OR: 5.90], 30.9% for ferrous gluconate [GAEs: 29.9%; OR: 11.06], 32.3% for ferrous sulfate without mucoproteose [GAEs: 30.2%; OR: 11.21], and 47.0% for ferrous fumarate [GAEs: 43.4%; OR: 19.87].

The differences in incidence of AEs between extended-release ferrous sulfate with mucoproteose and all other supplements except iron protein succinylate were statistically significant at $p < 0.001$. These findings are subject to some limitations as the designs and methodologies of the studies included show heterogeneity among them that has partially been counteracted by the large sample size provided by the substantial number of trials, which is considered a strength in tolerability studies.

Conclusion:
Extended-release ferrous sulfate with mucoproteose appears to be the best tolerated of the different oral iron supplements evaluated.

Introduction

Anemia is estimated to affect 2000 million people worldwide and is a serious public health problem with a range of social and economic repercussions[1,2]. Approximately 50% of anemia cases are associated with iron deficiency, although the proportion varies across populations and geographic regions[3]. In 2002, iron deficiency anemia was considered a major contributor to the global burden of disease[4] and is usually treated using oral iron supplements. Doses of 60–120 mg of elemental iron per day have been widely recommended in adults[5], though the daily dosage of iron should be determined according to the severity of

the anemia. The World Health Organization (WHO) recommends that the daily dose of iron should be administered at approximately 60 mg per intake to reduce adverse effects (AEs) and facilitate compliance[6]. The WHO also recommends the use of ferrous salts, which are considered the most effective and cost-effective treatment and preferable to ferric supplements, which show poorer absorption[6,7]. Ferrous supplements also have a higher bioavailability than ferric supplements[8–15] with ferrous sulfate being considered one of the oral treatments of choice[16–18] and being included on the WHO's list of essential drugs[6,7]. The above arguments have led some authors to suggest that ferric supplements should not be used[8,17]. On the other hand, intravenous iron has become standard in hemodialysis and is recommended in chemotherapy-induced anemia, as well as being useful in specific situations such as in cases of malabsorption (i.e., inflammatory bowel disease or gastric bypass), oral treatment intolerance, or when there is a need for rapid replacement of iron or significant and sustained blood loss[19,20].

Most oral iron supplements have been associated with erosive mucosal injury in the upper gastrointestinal tract as well as nausea, vomiting and epigastric discomfort[21–24] and other GAEs such as diarrhea and constipation[16,25–28]. A direct relationship has been observed between the number and severity of several AE and the dose of iron administered[19,25,27,29,30]. Adverse effects of this type may adversely affect treatment compliance and possibly lead patients to withdraw from treatment[3,31–33]. In order to reduce the problems of tolerability associated with oral iron treatment different formulations have been developed, the most common of which are connected with delayed release and/or protein addition[34]. Delayed release has been reported to improve gastrointestinal tolerability[18,19,35,36] and bioavailability[37]. Some of these formulations also include vitamin C to promote iron absorption, while others add mucoproteose, a substance that causes prolonged release of iron and protects the gastrointestinal mucosa[38]. Although much research has been carried out into the tolerability of different iron supplements, there has been no attempt to date to systematically review and compare tolerability across the various types of oral iron supplements. The aim of the present study was to carry out such a review based on available evidence relating to the tolerability of oral iron supplements regularly used to treat iron deficiency.

Methods

Data sources

In March 2009, we searched Embase, Medline, and the Cochrane Central Register of Controlled Trials for all dates up to and including January 2009 to identify potentially relevant publications. In order to maximize the number of publications meeting the selection criteria, we reviewed reference lists of key articles, and contacted the medical departments of companies marketing oral iron supplements to request any additional publications not identified during the electronic search.

Search strategy

Search terms used were: 'iron deficiency', 'oral iron', 'iron supplements', 'adverse effects', 'adverse events' 'tolerability' and 'safety'. These were applied to each of the following iron supplements: ferrous sulfate, ferrous sulfate with mucoproteose, iron protein succinylate, ferri-manitol-ovalbumin, ferrous fumarate, ferrous gluconate, and ferrous glycine sulfate. No limits were set in terms of time of publication, study design or dose of oral iron. The search was performed for publications in English, French, or Spanish. Articles in other languages for which a translation was available in one of the three study languages were also included.

If an article studied different doses of the same supplement in different patient groups[39–43], each treatment group was recorded as a separate study. The final number of studies was therefore equivalent to the number of different patient groups administered a given dose of any of the supplements studied.

Study selection

Titles and abstracts of all studies retrieved ($n = 10{,}982$) were reviewed by a single reviewer and clearly irrelevant publications were excluded. Five per cent of abstracts excluded at this point were reviewed by another reviewer to confirm their irrelevance. The original first reviewer then evaluated the full texts of the remaining articles ($n = 413$) to determine whether they were suitable for inclusion in the analysis. Any articles designated for exclusion at this stage were reviewed by a second reviewer to confirm exclusion. The full text of all articles remaining after this stage ($n = 80$) was reviewed by two reviewers to ensure they met inclusion criteria. Disagreements were resolved by consensus or third-party adjudication if necessary.

Eligibility criteria

Publications were included if the full text of the article was available and data were reported on any of the selected oral iron supplements. There were no restrictions on the type of clinical studies included as long as they reported adverse effects or events, dosage, duration and reason for treatment, participant characteristics, and study design. We also differentiated formulations of ferrous sulfate that

contain mucoproteose (Tardyferon, registered trade name of Pierre Fabre, Castres, France) from others which do not (Ferrogradumet, registered trade name of Teofarma SRL, Pavia, Italia; Feospan, registered trade name of Intrapharm Laboratories Ltd, Berkshire, UK, etc.) as reports suggest that the inclusion of mucoproteose is associated with improved gastrointestinal tolerability[38,44].

In order to avoid incorrectly attributing AEs to oral iron supplements, publications in which supplements were associated with folic acid, were part of multivitamins or were administered together with other treatments (e.g., erythropoietin) were excluded. As intolerance to iron supplements manifests mainly in the form of gastrointestinal disorders, we excluded studies that evaluated oral iron supplements in patients with gastrointestinal diseases.

Data extraction

For each study included, one reviewer extracted the data and a second reviewer confirmed the selected data. Any potential discrepancies were resolved by consensus and, if necessary, by referring to a third reviewer. A pre-developed pro-forma was used to extract descriptive data on study design, reason for treatment, number of patients included, dose of elemental iron studied, period of treatment and number of overall and gastrointestinal adverse effects described.

Data synthesis

To establish the incidence of AEs in each study, we considered the number of patients experiencing at least one AE in relation to all patients in the safety analysis. To ensure that the results were relevant for clinical practice and to establish a comparison between different iron supplements, we conducted a second analysis in which only studies evaluating a daily dose of elemental iron between 80 and 120 mg were included. This is the most frequently used therapeutic dose range[45] which meets the recommendations of several health organizations for oral iron supplements for the treatment of iron deficiency anemia[3,5]. We also performed a separate analysis of data in the publications included to determine the comparative incidence of gastrointestinal adverse effects. Events studied included nausea, vomiting, diarrhea, bloating, and constipation. This additional analysis was also performed in those studies reporting a daily dose range of elemental iron between 80 and 120 mg.

Statistical analysis

A descriptive analysis of the collected data was performed. Data were analyzed in terms of general AEs and gastrointestinal AEs for all studies and for the subgroup of studies which used between 80 and 120 mg of daily elemental iron.

A logistic regression model was used to compare the odds ratio (OR) for intolerance among the various oral iron formulations. We used the log-linear quasi-binomial procedure by GAM library (Analysis of Deviance for a Generalized Additive Model) to fit over-dispersed logistic regression models. The model weighted each study in proportion to sample size while allowing for heterogeneity between studies by including a dispersion variable[46–48]. All analyses were weighted by the number of patients in each study and supplement showing the best tolerability was used as the reference category. Statistical significance was set at $p \leq 0.05$ and analyses were performed using the open-source statistical language and environment R 2.11.1[49].

Results

Study selection

The literature search identified 11,354 publications of which 413 were selected for a full text review. 333 of these were excluded for the reasons indicated in Figure 1. In total, 111 studies (included in 80 publications) met the selection criteria for inclusion in this analysis.

Study characteristics

The 111 studies selected, 82 of them being randomized, provided data on tolerability in 10,695 patients. Of the selected studies, 104 provided data specifically for gastrointestinal tolerability and 57 were carried out with a daily iron dose between 80 and 120 mg and 52 of those studies reported data on gastrointestinal tolerability. A summary of the study characteristics by oral iron supplement is shown in Table 1 and data on study design, daily dose of iron administered, indication for administration of oral iron, number of patients in each study, and the number of patients experiencing any type of AE and GAE are reported in Table 2 (2A–F).

Of the studies selected, 88.3% ($n = 98$) reported tolerability in terms of adverse effects; for iron protein succinylate, ferrous gluconate, and ferrous glycine sulfate only adverse effects were reported. The remaining studies ($n = 13$) referred adverse events. The latter represented 7.04% of the total population analyzed.

Ferri-manitol-ovalbumin was excluded from the analysis due to the small number of publications obtained were suitable for inclusion. The pharmaceutical companies marketing this oral iron supplement did not provide any additional studies despite our requests.

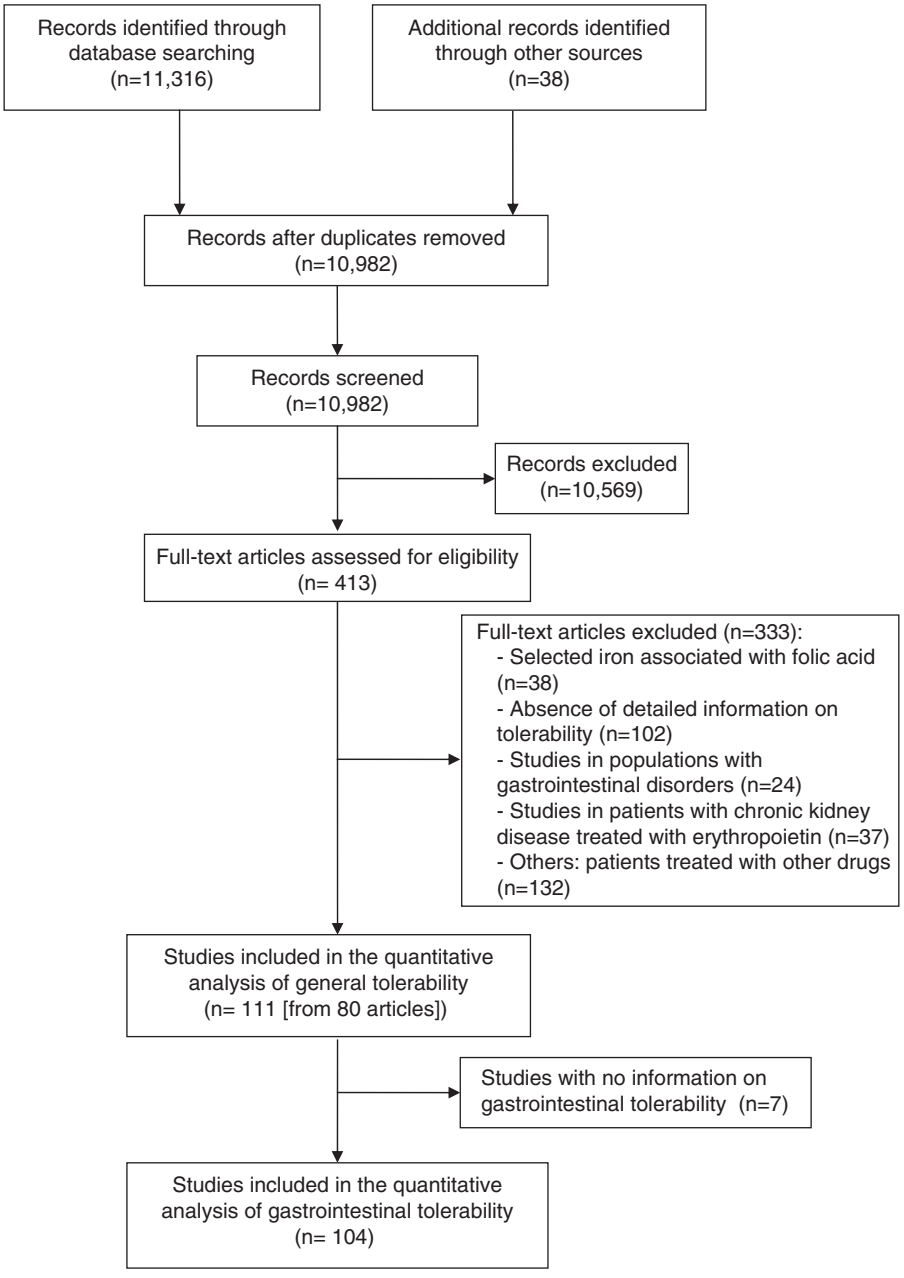

Figure 1. Flow diagram of study selection.
n = number of publications.

Table 1. Summary of data analyzed.

Oral iron supplement	Studies (*n*)	Total patients (*n*)	Weighted mean dose (mg iron/day)	Total AEs registered (*n*)	Total GAEs registered (*n*)*
Iron protein succinylate	10	4198	88	308	295
Ferrous sulfate	40	3271	120	1056	869
Ferrous sulfate plus mucoproteose	32	1293	105	53	48
Ferrous fumarate	11	757	105	356	298
Ferrous glycine sulfate	8	604	121	142	112
Ferrous gluconate	10	572	175	177	171

*Not all the studies specifically reported GAEs.

Table 2. Tolerability of oral iron formulations analyzed in the study.

Study	Comparator	Randomized/ blinding	Patients (*n*)	Indication†	Dose (mg iron/day)	Duration (days)	AEs (*n*)	GAEs (*n*)
A: Tolerability of ferrous sulfate.								
Kerr, 1958[50]	Other ferrous salts	Yes/double blind	81	Other	105	98	20	20
Hood,1960[51]	Control	Yes/open label	23	Prophylaxis of iron deficiency in pregnancy	120	35	8	8
Hood,1960[51]	Control	Yes/open label	22	Prophylaxis of iron deficiency in pregnancy	30	39	4	4
Hallberg,1966[39]	Placebo	Yes/double blind	175	Other	222	15	40	40
Hallberg,1966[39]	Placebo, ferrous fumarate, Ferrous gluconate	Yes/double blind	111	Other	222	17	31	31
Hallberg,1966[39]	Placebo, ferrous glycine sulfate, ferrous gluconate	Yes/double blind	170	Other	180	21	45	45
Symonds,1969[40]	Ferrous sulfate, placebo, ferrous gluconate Intravenous iron	Yes/double blind	25	Gestational anemia	105	30	7	7
Elwood, 1970[41]	Ferrous sulfate, ferrous fumarate, ferrous carbonate	Yes/single blind	66	Iron deficiency anemia	105	56	17	–
Elwood, 1970[41]	Ferrous sulfate, ferrous fumarate, ferrous carbonate	Yes/single blind	107	Iron deficiency anemia	45–90	56	35	–
Elwood, 1970[41]	Ferrous sulfate, ferrous fumarate, ferrous carbonate	Yes/single blind	34	Iron deficiency anemia	100	56	14	–
Kirchhoff, 1978[52]	Ferrous sulfate	Yes/double blind	24	Iron deficiency	160	14	4	4
Levy, 1978[53]	Placebo, ferrous sulfate	Yes/open label	107	Others (healthy adults)	100	10	61	61
Leslie, 1979[54]	Ferrous glycine sulfate	Yes/open label	22	Iron deficiency anemia	45	28	5	5
Sas, 1984[55]	Ferric (III) dextrin complex, ferrous fumarate	Yes/double blind	20	Iron deficiency anemia	100	84	2	2
Brock, 1985[56]	Ferrous sulfate	Yes/single blind	272	Other	50	56	136	124
Gordeuk, 1987[57]	Carbonyl iron	Yes/double blind	24	Iron deficiency anemia	180	7	20	20
Coplin, 1991[58]	Ferrous glycine sulfate	Yes/double blind	38	Other	50	14	26	25
Devasthali, 1991[59]	Carbonyl iron	Yes/double blind	25	Iron deficiency anemia	100	112	20	20
Jacobs, 1993[12]	Ferric polymaltose	Yes/open label	45	Iron deficiency	120	84	11	–
Liguori, 1993[60]	Iron protein succinylate (ITF282)	Yes/double blind, double dummy	539	Iron deficiency/Iron deficiency anemia	105	60	127	100
Köpcke, 1995[34]	Iron protein succinylate (ITF282)	Yes/double blind, double dummy	84	Iron deficiency anemia	105	60	9	–
Al-Momen, 1996[61]	Intravenous iron sucrose complex (ISC)	Yes/open label	59	Gestational anemia	180	105	22	18
Bruner, 1996[62]	Placebo	Yes/double blind	34	Other	260	56	22	22
Casparis, 1996[63]	Ferrous gluconate, iron protein succinylate	Yes/open	10	Gestational anemia/Other	105	30	1	0
Ekström, 1996[64]	No	Yes/open label	69	Gestational anemia	120	84	15	15
Surico, 1998[65]	Iron gluconate	No/open label	34	Other-children	4.25 mg/kg	1	14	14
Jacobs, 2000[66]	IPC, IPC + glycerophosphate, ferrous sulfate	Yes/open label	47	Iron deficiency anemia	100	84	21	9
Pujol-Farriols, 2002[67]	Iron protein succinylate	No/open label	30	Iron deficiency anemia	210	180	4	4
Ahmed, 2003[68]	Ferrous sulfate	Yes/open label	100	Iron deficiency anemia in children	6 mg/kg	42	15	15
Makrides, 2003[69]	Placebo	Yes/double blind	204	Others	20	28	100	100
De Silva, 2005[70]	No	No/open label	14	Iron deficiency	120+	28	4	4

(*continued*)

Table 2. Continued.

Study	Comparator	Randomized/ blinding	Patients (*n*)	Indication†	Dose (mg iron/day)	Duration (days)	AEs (*n*)	GAEs (*n*)
Van Wyck, 2005[71]	IV iron sucrose	Yes/open label	91	Iron deficiency anemia	195	56	33*	33**
Agarwal, 2006[72]	Ferric gluconate iron (IV)	Yes/open label	45	Iron deficiency	195	42	9*	9**
Bhandal, 2006[73]	IV ferrous sucrose	Yes/open label	21	Iron deficiency anemia	80	42	7*	7**
Christofides, 2006[74]	Ferrous fumarate, ferric pyrophosphate	Yes/double blind	24	Iron deficiency anemia in children	12.5 mg/kg	56	14	14
Van Wyck, 2007[75]	IV ferric carboxymaltose	Yes/open label	178	Gestational anemia	195	42	54*	43**
Melamed, 2007[76]	Ferrous fumarate, ferric polymaltose, ferric bisglycinate	Yes/open label	54	Gestational anemia	100	90–180	29	29
Muneyyirci, 2007[77]	Goserelin acetate, ferrous sulfate	Yes/double blind	56	Iron deficiency	195	84	16*	–
Breymann, 2008[78]	IV ferric carboxymaltose	Yes/open label	117	Postpartum anemia	40	84	26*	9**
Westad, 2008[79]	IV iron sucrose + ferrous sulfate	Yes/open label	70	Postpartum anemia	200	84	8*	8**
TOTAL			**3271**				**1056**	
B: Tolerability of ferrous sulfate plus mucoproteose.								
Siegenthaler, 1972[80]	No	No/open label	3	Iron deficiency	80	21	0	0
Largiadèr, 1973[81]	No	No/open label	24	Iron deficiency/deficiency anemia	80–160	5–39	0	0
Kozlowska, 1974[82]	No	No/open label	50	Iron deficiency anemia	80–160	42	0	0
Schindler, 1975[38]	No	No/open label	53	Iron deficiency anemia	160	7–28	2	2
Holowiecki, 1976[83]	No	No/open label	51	Iron deficiency anemia	160	28–48	4*	4**
Schusselé, 1976[84]	No	No/open label	40	Iron deficiency anemia	80–160	21	1	1
Díaz-Rubio, 1976[85]	No	No/open label	40	Iron deficiency anemia/other	80–160	42	0	0
Draganski, 1977[86]	No	No/open label	33	Iron deficiency anemia	80	21–84	0	0
Hauser, 1977[87]	No	No/open label	250	Gestational anemia	80	48–150	4	0
Thomann, 1977[88]	No	No/open label	20	Iron deficiency anemia	80	42–84	0	0
Germann, 1978[89]	No	No/open label	37	Iron deficiency anemia	80	112	0	0
Müldner, 1978[90]	No	No/open label	40	Iron deficiency anemia	80	42–84	0	0
Popko, 1978[91]	No	No/open label	21	Iron deficiency anemia/other	80	14	0	0
Kirchhoff, 1978[52]	Ferrous sulfate	Yes/double blind	24	Iron deficiency	160	14	0	0
Steger, 1978[92]	No	No/open label	30	Iron deficiency anemia	80	84	0	0
Hellerer, 1978[93]	No	No/open label	35	Other	80	21	0	0
Metzger, 1978[44]	No	No/open label	30	Iron deficiency/iron deficiency anemia	80	28	0	0
Oehlert, 1978[94]	No	No/open label	40	Iron deficiency anemia	80	14–21	0	0
Müldner, 1979[95]	Placebo	Yes/double blind	29	Iron deficiency	80	28	0	0
Gerlach, 1979[96]	No	No/open label	49	Iron deficiency anemia	80	56	0	0
Gaultier, 1979[97]	No	No/open label	41	Iron deficiency anemia	80–160	60–240	3	3
Junck, 1980[98]	Ferrous sulfate + folic acid	Yes/open label	20	Gestational anemia	80	56	0	0
Buzi, 1980[99]	Ferrous fumarate	Yes/double blind	32	Iron deficiency	80	30	3	2
Bernát, 1984[100]	No	No/open label	32	Iron deficiency	160	196	7	7
Ifrah, 1986[101]	No	No/open label	22	Iron deficiency anemia	160	90	3	3
Pengloan, 1986[102]	Ferrous succinate	Yes/open label	14	Iron deficiency anemia	80	180	0	0
Pejtsik, 1987[103]	No	No/open label	99	Iron deficiency/gestational anemia	160	56	9	9
Bernard, 1989[104]	Control	No/open label	39	Iron deficiency	80	56	1*	1**
Bernard, 1989[104]	Control	No/open label	10	Iron deficiency	160	56	1*	1**
Mára, 2001[105]	Control	Yes/open label	40	Other	80	90	0	0
Krafft, 2005[106]	Placebo	Yes/double blind	28	Other	80	84	12*	12**
Konofal, 2008[107]	Placebo	Yes/double blind	17	Other (children)	80	84	3*	3**
TOTAL			**1293**				**53**	

C: Tolerability of iron protein succinylate.								
De Renzo, 1987[108]	Ferritin compound	Yes/open label	25	Iron deficiency anemia	80	60	6	6
Scremin, 1988[109]	Iron gluconate	Yes/open label	15	Iron deficiency	80	30	2	2
Sallusto, 1990[110]	No	No/open label	2996	Other	80	30-120	183	175
Careddu, 1993[111]	Iron polystyrene sulfonate	Yes/double blind double dummy	256	Iron deficiency/iron deficiency anemia – children	60–120	60	13	13
Liguori, 1993[60]	Ferrous sulfate	Yes/double blind double dummy	549	Gestational anemia/other	120	60	63	63
Köpcke, 1995[34]	Iron sulfate	Yes/double blind	85	Iron deficiency anemia	120	60	8	8
Casparis, 1996[63]	Ferrous sulfate, ferrous gluconate	Yes/open label	10	Gestational anemia/other	80	30	4	3
Haliotis, 1998[112]	Iron hydroxide polymaltose complex	Yes/open label	50	Iron deficiency/iron deficiency anemia – children	4 mg/kg (≤80)	60	6	6
Pujol-Farriols, 2002[67]	Ferrous sulfate	No/open label	30	Iron deficiency anemia	80	180	1	1
Juárez-Vázquez, 2002[113]	Iron protein succinylate + folic acid	Yes/double blind	182	Iron deficiency anemia	80	60	22	18
TOTAL			**4198**				**308**	
D: Tolerability of ferrous fumarate.								
Hallberg, 1966[39]	Placebo, ferrous sulfate, ferrous gluconate	Yes/double blind	110	Other	222	18	29	29
Elwood, 1970[41]	Ferrous sulfate, ferrous carbonate	Yes/single blind	70	Iron deficiency anemia	100	56	17	–
Buzi, 1980[99]	Ferrous sulfate + mucoproteose	Yes/double blind	32	Iron deficiency	132	30	16	15
Black, 1981[114]	Ferrous glycine sulfate	Yes/open label	10	Iron deficiency anemia	195	30	0	0
Aronstam, 1982[42]	Ferrous glycine sulfate	Yes/single blind	38	Iron deficiency anemia	100	28	13	13
Adsul, 2005[115]	Carbonyl iron	Yes/double blind	30	Iron deficiency anemia	100	84	12*	9**
Milman, 2006[43]	Ferrous fumarate	Yes/double blind	71	Iron deficiency	20	98	37	0
Milman, 2006[43]	Ferrous fumarate	Yes/double blind	68	Iron deficiency	40	98	34	34
Milman, 2006[43]	Ferrous fumarate	Yes/double blind	79	Iron deficiency	60	98	46	46
Milman, 2006[43]	Ferrous fumarate	Yes/double blind	75	Iron deficiency	80	98	54	54
Melamed, 2007[76]	Ferrous sulfate, ferric polymaltose, ferric bisglycinate	Yes/open label	174	Gestational anemia	100	90–180	98	98
TOTAL			**757**				**356**	
E: Tolerability of ferrous glycine sulfate.								
Hallberg, 1966[39]	Placebo, ferrous sulfate, ferrous gluconate	Yes/double blind	180	Other	180	22	44	44
Leslie, 1979[54]	Ferrous sulfate	Yes/open label	23	Iron deficiency anemia	100	28	3	3
Black, 1981[114]	Ferrous fumarate	Yes/open label	20	Iron deficiency anemia	100	30	0	0
Aronstam, 1982[42]	Ferrous fumarate	Yes/single blind	38	Iron deficiency anemia	100	28	10	10
Coplin,1991[58]	Ferrous sulfate	Yes/double blind	38	Other	50	14	25	23
Liu, 2004[116]	Ferrous fumarate	Yes/open label	36	Iron deficiency anemia	150	84	7	7
Kavakli, 2004[117]	Iron polymaltose complex	Yes/open label	39	Iron deficiency anemia (children)	2–6 mg/kg	360	6	5
Radtke, 2004[118]	Placebo	Yes/open label	230	Other	100	168	47	20
TOTAL			**604**				**142**	
F: Tolerability of ferrous gluconate.								
Kerr, 1958[50]	Placebo, other ferrous salts	Yes/double blind	88	Other	105	98	30	30
Hallberg, 1966[39]	Placebo, ferrous sulfate, ferrous fumarate	Yes/double blind	111	Other	222	19	35	35
Hallberg, 1966[39]	Placebo, ferrous sulfate, ferrous glycine sulfate	Yes/double blind	178	Other	180	23	48	48
Symonds, 1969[40]	Ferrous sulfate, placebo, intravenous iron	Yes/open label	24	Gestational anemia	108	≥28	7	7
Scremin, 1988[109]	Iron protein succinylate	Yes/open label	15	Iron deficiency anemia	125	30	4	4

(*continued*)

Table 2. Continued.

Study	Comparator	Randomized/ blinding	Patients (*n*)	Indication†	Dose (mg iron/day)	Duration (days)	AEs (*n*)	GAEs (*n*)
Casparis, 1996[63]	Ferrous sulfate, iron protein succinylate	Yes/open label	10	Iron deficiency anemia	75 (liquid)	30	0	0
Casparis, 1996*[63]	Ferrous sulfate, iron protein succinylate	Yes/open label	10	Gestational anemia/Other	80 (solid)	30	1	1
Rimon, 2005[119]	Ferrous gluconate	Yes/open label	30	Iron deficiency anemia	50	60	20	20
Rimon, 2005[119]	Ferrous gluconate	Yes/open label	30	Iron deficiency anemia	15	60	13	13
Wall, 2005[120]	Ferrous caseinate, ferrous sulfate	Yes/double blind	76	Iron deficiency	3 mg/kg (children)	90	19	13
TOTAL			**572**				**177**	

IPC, Iron polymaltose complex; AEs, adverse effects; GAEs, gastrointestinal adverse effects.
*Adverse events; **gastrointestinal adverse events; †indication: Other (i.e.: at risk for anemia due to blood donation; pregnancy; anemia secondary to other diseases; +, Estimated dose.

Study findings

The graph showing the incidence of AEs by iron supplement and study is shown in Figure 2 and the figures for the overall tolerability of each studied supplement is depicted in Figure 3. As is to be expected, given that GAEs are the most common adverse reactions observed with iron supplements, the relative incidence of GAEs was similar to that shown in Figure 3. Frequencies recorded for GAEs were 3.7% for ferrous sulfate with mucoproteose, 7.0% for iron protein succinylate, 18.5% for ferrous glycine sulfate, 29.9% for ferrous gluconate, 30.2% for ferrous sulfate, and 43.4% for ferrous fumarate.

By comparing the frequencies obtained, we calculated the odds ratio for experiencing an AE with each of the supplements studied. As it had the lowest incidence of AEs, extended-release ferrous sulfate with mucoproteose was used as the reference supplement. The results of this analysis are shown in Table 3, both for when all studies were incorporated and when only studies using a daily dose between 80 and 120 mg were included. Odds ratios ranged from 1.85 (95% CI 0.85–4.05) and 2.73 (95% CI 0.79–9.49) for iron protein succinylate in the 'All dose' and '80–120 mg/day' groups, respectively, to 20.8 (95% CI 9.21–46.84) and 34.3 (95% CI 9.10–129.07) in the same groups for ferrous fumarate. All differences with the reference supplement were statistically significant at $p < 0.01$ except for iron protein succinylate.

Discussion

This systematic review is, to our knowledge, the first to exhaustively evaluate and compare the tolerability of different, widely-used iron supplements. We found that extended-release ferrous sulfate with mucoproteose showed the best tolerability profile. This finding applied to both kinds of adverse effects, general and gastrointestinal. Ferrous fumarate had the highest rates of general and gastrointestinal AEs. Similar results were observed when analyzing the most regularly used dose ranges.

Our findings are in line with the results of other studies which have shown that extended-release ferrous sulfate with mucoproteose is well-tolerated and effective in patients with gastrointestinal disorders[121–123]. The lower incidence of AEs seen with this compound can be attributed to its galenical formulation, which leads to an extended release of iron and prevents the release of large quantities of elemental iron into the stomach. The effect is reinforced by the use of the gastrointestinal protector mucoproteose, a substance rich in amino sugars which protects the gastrointestinal mucosa, as reported for other proteins in oral iron formulations[29,124]. It is important to underline the fact that problems of adherence limit the

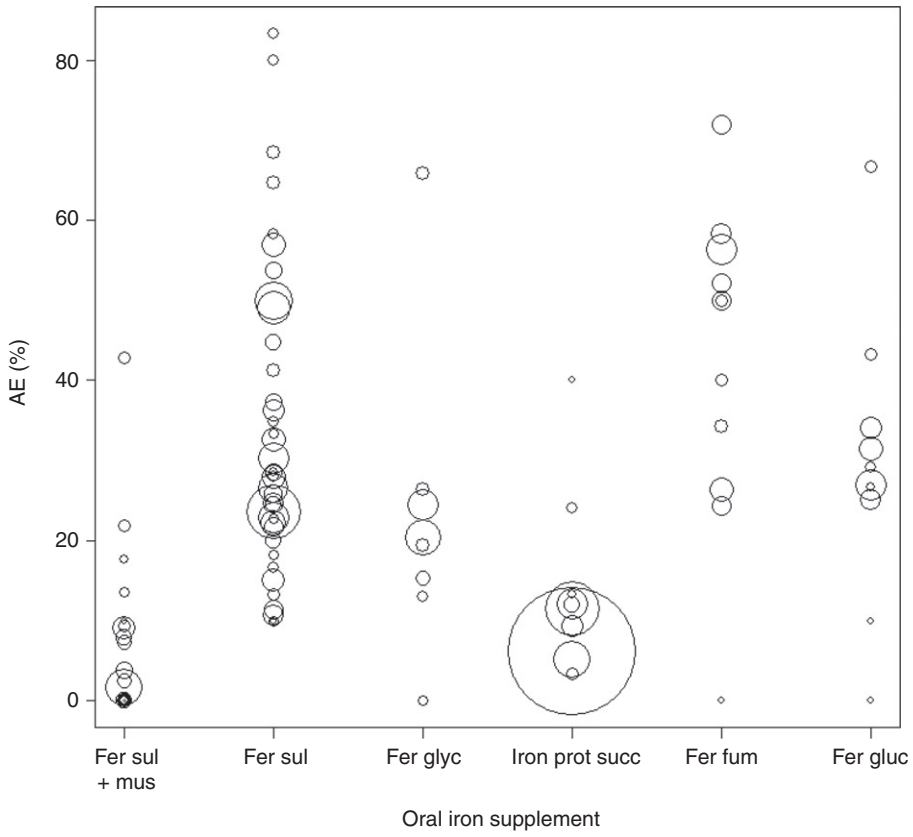

Figure 2. AE percentage by oral iron supplement in the selected studies. Circle area represents study sample size. Fer sul + muc: ferrous sulfate plus mucoproteose; Fer sul: ferrous sulfate (without mucoproteose); Fer glyc: ferrous glycine sulfate; Iron prot succ: iron protein succinylate; Fer fum: ferrous fumarate; Fer gluc: ferrous gluconate.

effectiveness of iron supplementation programs[125,126] with reports suggesting adherence rates of 40–60% in the treatment and prevention of iron deficiency anemia[84,127,128].

Earlier reviews assessed other aspects of iron supplements[125], or their efficacy in specific populations, such as pregnant women[28], or only focussed on one supplement[34]. Likewise, the fact that studies in which iron supplements were combined with other treatments were excluded from the analysis is likely to increase the reliability of the reported results and ensure that the AEs recorded were mainly associated with the supplement administered.

Besides tolerability, the most important aspect of a treatment is its efficacy. There is a large body of evidence which confirms the efficacy of the prolonged release formulations analyzed in the present study, including ferrous sulfate plus mucoproteose[104–106,122,129], ferrous glycine sulfate[118], iron protein succynilate[34,60,113], and ferrous sulfate extended-release[60,67]. Of particular interest is a recent publication by Donnez *et al.*[129] in which ferrous sulfate plus mucoproteose administered at a daily dosage of 80 mg of iron in a randomized, double-blind, controlled trial was shown to be effective in restoring mean hemoglobin levels in women with sustained menorrhagia secondary to uterine fibroids.

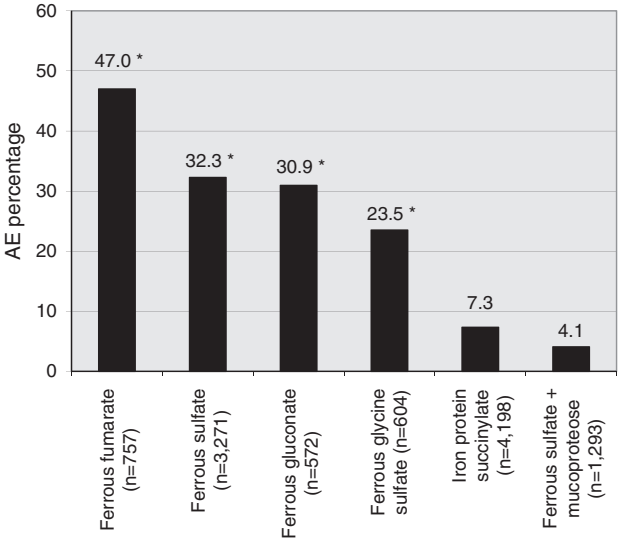

Figure 3. Overall tolerability. Tolerability of the iron supplements studied. The "*n*" shows the sample size of each iron supplement in which frequency has been calculated. $*p < 0.001$ compared to the iron supplement of reference (ferrous sulfate plus mucoproteose).

Table 3. Relative risk of any type of adverse effect.
Studies with any dose and those using exclusively doses of 80–120 mg/day.

Oral iron supplement	All doses		80–120 mg/day	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Ferrous sulfate + mucoproteose	1 (reference value)	–	1 (reference value)	–
Iron protein succinylate	1.85 (0.85–4.05)	0.126	2.73 (0.79–9.49)	0.119
Ferrous glycine sulfate	7.19 (3.00–17.24)	<0.001	8.15 (1.92–34.57)	0.006
Ferrous gluconate	10.48 (4.44–24.74)	<0.001	15.42 (3.03–78.52)	0.002
Ferrous sulfate	11.15 (5.29–23.54)	<0.001	14.27 (4.11–49.57)	<0.001
Ferrous fumarate	20.77 (9.21–46.84)	<0.001	34.26 (9.10–129.07)	<0.001

Limitations

This systematic review suffers from limitations related to the articles from which data were extracted. One limitation is that doses differed between the articles reviewed according to indication and severity of the iron deficiency anemia treated, though this limitation was common to all the supplements tested. In order to minimize the possible effect of these differences in dose, we performed a second analysis in which we included only those studies that analyzed the dose most regularly used in clinical practice (80–120 mg/day of elemental iron)[45]. The results of this additional analysis were essentially identical to those of the main analysis, suggesting that the different doses studied in the present systematic review do not seem to influence the study results.

The variety of designs and methodologies used in the studies included for analysis was another limitation. While it may have been preferable to include only randomized controlled clinical trials in the analysis, such an approach would have severely limited the number of patients that could be included, and may have made the analysis impractical. Furthermore, when studying tolerability, large sample sizes are an advantage. It should also be noted that heterogeneity in study design and methods was common to all of the supplements studied so it may have had little effect on the relative frequencies of AEs. Sufficient data on AEs were available for all supplements except ferri-manitol-ovalbumin, which had to be excluded from the analysis.

Finally, as the main objective was to assess tolerability, we included studies reporting adverse effects or adverse events. Both types of reaction were studied, though the great majority of studies reported adverse effects. We also examined studies reporting adverse events and those reporting adverse effects separately, but observed similar trends to those seen in the main analysis. Nevertheless, as the number of patients in studies reporting adverse events was too small for a tolerability analysis, the results have not been reported.

It would be of interest for future studies to confirm the present results in a large, randomized, double-blind trial to compare the different iron supplements analyzed here and to evaluate treatment compliance. Moreover, as iron deficiency is a worldwide health problem, cost-effectiveness studies taking into account efficacy, adverse effects and their costs and the influence of compliance on avoiding health complications would provide very useful information for decision makers.

Conclusion

This systematic review has shown that extended-release ferrous sulfate with mucoproteose is the best tolerated of the supplements studied and could be considered as an advisable treatment option for iron deficiency. Better tolerability might lead to improved adherence due to fewer withdrawals from treatment, and thereby increase the effectiveness of iron supplementation leading to a positive impact on quality of life.

Transparency

Declaration of interest
This work was funded by Pierre Fabre Ibérica, S.A. All authors contributed to the conception and design of the study and the interpretation of data, and also had full access to all of the study data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of financial/other relationships
M.J.C-H., M.C-R., J.H-P., and L.P-E. have no relevant financial relationships to disclose. J.M. has disclosed that he is employed full-time by Pierre Fabre Ibérica S.A., as medical advisor. C.C-B. has disclosed that he has received a fee for a lecture to Pierre Fabre employees. S.P. has been consultant to and on the speakers' bureau of the following: Sanofi Pasteur, MSD, Pfizer, Bayer Schering Pharma, Servier, Lilly, Pierre Fabre, Daiichi-Sankyo, Roche, Warner Chilcott, Amgen, Arkopharma and Boehringer-Ingelheim. CMRO peer reviewers of this manuscript have no relevant financial relationships to disclose.

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