Current PSYCHIATRY

Iron deficiency in psychiatric patients

Evidence suggests iron replacement might improve psychiatric symptoms

Nutritional deficiencies are one of the many causes of or contributors to symptoms in patients with psychiatric disorders. In this article, we discuss the prevalence of iron deficiency and its link to poor mental health, and how proper treatment may improve psychiatric symptoms. We also offer suggestions for how and when to test for and treat iron deficiency in psychiatric patients.

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A common condition

Iron deficiency is the most common mineral deficiency in the world. According to the World Health Organization (WHO), approximately 25% of the global population is anemic and nearly one-half of those cases are the result of iron deficiency.[1] While the WHO has published guidelines defining iron deficiency as it relates to ferritin levels (<15 ug/L in adults and <12 ug/L in children), this estimate might be low.[2,3] Mei et al[2] found that hemoglobin and soluble transferrin receptors can be used to determine iron-deficient erythropoiesis, which indicates a physiological definition of iron deficiency. According to a study of children and nonpregnant women by Mei et al,[2] children with ferritin levels <20 ug/L and women with ferritin levels <25 ug/L should be considered iron-deficient. If replicated, this study suggests the prevalence of iron deficiency is higher than currently estimated.[2] Overall, an estimated 1.2 billion people worldwide have iron-deficiency anemia.[4]

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Iron deficiency

Clinical Point

Research suggests an association between iron deficiency and depression, anxiety, and schizophrenia

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Additionally, patients can be iron deficient without being anemic, a condition thought to be at least twice as common.[4]

Essential for brain function

Research shows the importance of iron to proper brain function.[5] Iron deficiency in pregnant women is associated with significant neuropsychological impairments in neonates. Rodent studies have demonstrated the importance of iron and the effects of iron deficiency on the hippocampus, corpus striatum, and production of monoamines.[5] Specifically, iron is a necessary cofactor in the enzymes tryptophan hydroxylase and tyrosine hydroxylase, which produce serotonin, dopamine, and norepinephrine. In rodent studies, monoamine deficits secondary to iron deficiency persist into adulthood even with iron supplementation, which highlights the importance of preventing iron deficiency during pregnancy and early life.[5] While most research has focused on the impact of iron deficiency in infancy and early childhood, iron deficiency has an ongoing impact into adulthood, even if treated.[6]

Iron deficiency and psychiatric symptoms

Current research suggests an association between iron deficiency or low ferritin levels and psychiatric disorders, specifically depression, anxiety, and schizophrenia. In a web survey of 11,876 adults, Hidese et al[7] found an association between a self-reported history of iron deficiency anemia and a self-reported history of depression. Another study of 528 municipal employees found an association between low serum ferritin concentrations and a high prevalence of depressive symptoms among men; no statistically significant association was detected in women.[8] In an analysis of the Taiwan National Health Insurance Database from 2000 to 2012, Lee et al[9] found a statistically significant increased risk of anxiety disorders, depression, sleep disorders, and psychotic disorders in patients with iron deficiency anemia after controlling for multiple confounders. Xu et al[10] used quantitative susceptibility mapping to assess the iron status in certain regions of the brain of 30 patients with first-episode psychosis. They found lower levels of iron in the bilateral substantia nigra, left red nucleus, and left thalamus compared to healthy controls.[10] Kim et al[11] found an association between iron deficiency and more severe negative symptoms in 121 patients with first-episode psychosis, which supports the hypothesis that iron deficiency may alter dopamine transmission in the brain.

Iron deficiency has been associated with psychopathology across the lifespan. In a population-based study in Taiwan, Chen et al[12] found an association between iron deficiency anemia and psychiatric disorders in children and adolescents, including mood disorders, autism spectrum disorder, attention-deficit/hyperactivity disorder, and developmental disorders. At the other end of the age spectrum, in a survey of 1,875 older adults in England, Stewart et al[13] found an association between low ferritin levels (<45 ng/mL) and depressive symptoms after adjusting for demographic factors and overall health status.

In addition to specific psychiatric disorders and symptoms, iron deficiency is often associated with nonspecific symptoms such as fatigue.[14] Fatigue is a symptom of numerous psychiatric disorders and is included in the DSM diagnostic criteria for major depressive disorder and generalized anxiety disorder.[15]

Iron supplementation might improve psychiatric symptoms

Some evidence suggests that using iron supplementation to treat iron deficiency can improve psychiatric symptoms. In a 2013 systematic literature review of 10 studies, Greig et al[16] found a link between low iron status and poor cognition, poor mental health scores, and fatigue among women of childbearing age. In this review, 7 studies demonstrated improvement in cognition and 3 demonstrated improvement in mental health with iron supplementation.[16] In a 2021 prospective study, 19 children and adolescents age 6 to 15 who had serum ferritin levels <30 ng/mL were treated with

oral iron supplementation for 12 weeks.[17] Participants showed significant improvements in sleep quality, depressive symptoms, and general mood as assessed via the Pittsburgh Sleep Quality Index, Center for Epidemiologic Studies Depression Scale, and Profile of Mood States (POMS) questionnaires, respectively.[17] A randomized controlled trial of 219 female soldiers who were given iron supplementation or placebo for 8 weeks during basic combat training found that compared to placebo, iron supplementation led to improvements in mood as measured by the POMS questionnaire.[18] Lastly, in a 2016 observational study of 412 adult psychiatric patients, Kassir[19] found most patients (81%) had iron deficiency, defined as a transferrin saturation coefficient <30% or serum ferritin <100 ng/mL. Although these cutoffs are not considered standard and thus may have overrepresented the percentage of patients considered iron-deficient, more than one-half of patients considered iron-deficient in this study experienced a reduction or elimination of psychiatric symptoms following treatment with iron supplementation and/or psychotropic medications.[19]

Individuals with iron deficiency without anemia also may see improvement in psychiatric symptoms with iron treatment. In a 2018 systematic review, Houston et al[20] evaluated iron supplementation in 1,170 adults who were iron-deficient but not anemic. They found that in these patients, fatigue significantly improved but physical capacity did not.[20] Additionally, 2 other studies found iron treatment improved fatigue in nonanemic women.[21,22] In a 2016 systematic review, Pratt et al[23] concluded, "There is emerging evidence that … nonanemic iron deficiency … is a disease in its own right, deserving of further research in the development of strategies for detection and treatment." Al-Naseem et al[24] suggested severity distinguishes iron deficiency with and without anemia.

Your role in assessing and treating iron deficiency

Testing for and treating iron deficiency generally is not a part of routine psychiatric practice. This might be due to apathy given the pervasiveness of iron deficiency, a belief that iron deficiency should be managed by primary care physicians, or a lack of familiarity with how to treat it and the benefits of such treatment for psychiatric patients. However, assessing for and treating iron deficiency in psychiatric patients is important, especially for individuals who are highly susceptible to inadequate iron levels. People at risk for iron deficiency include pregnant women, infants, young children, women with heavy menstrual bleeding, frequent blood donors, patients with cancer, individuals who have gastrointestinal (GI) surgeries or disorders, and those with heart failure.[25]

Assessment. Iron status can be assessed through an iron studies panel. Because a patient can have iron deficiency without anemia, a complete blood count (CBC) alone does not suffice.[26] The iron panel includes serum iron, serum ferritin, serum transferrin or total iron-binding capacity (TIBC), and calculated transferrin saturation (TSAT), which is the ratio of serum iron to TIBC.

Iron deficiency is diagnosed if ferritin is <30 ng/mL, regardless of the hemoglobin concentration or underlying condition, and confirmed by a low TSAT.[26] In most guidelines, the cutoff value for TSAT for iron deficiency is <20%. Because the TSAT can be influenced by iron supplements or iron-rich foods, wait several hours to obtain blood after a patient takes an oral iron supplement or eats iron-rich foods. If desired, clinicians can use either ferritin or TSAT alone to diagnose iron deficiency. However, because ferritin can be falsely normal in inflammatory conditions such as obesity and infection, a TSAT may be needed to confirm iron deficiency if there is a high clinical suspicion despite a normal ferritin level.[26]

Treatment. If iron deficiency is confirmed, instruct your patient to follow up with their primary care physician or the appropriate specialist to evaluate for any underlying etiologies.

Iron deficiency should be treated with supplementation because diet alone is insufficient for replenishing iron stores.

continued

Clinical Point

Oral iron replacement is effective, safe, easy to obtain, and easy to administer

Iron deficiency

Clinical Point

Using a liquid form of iron supplements may help reduce adverse effects because it can be easily titrated

Table

Types of iron supplements

Supplement	Elemental iron content	Efficacy/cost	Adverse effects
Ferrous sulfate	20% to 30% elemental iron per mg ferrous sulfate salt, but can vary by manufacturer[27]	Least expensive, most common[30]	Taking with food can increase tolerability but decrease absorption by 40% to 66%[31]
Ferrous gluconate	10% to 14% elemental iron per mg ferrous fumarate salt[27]	More expensive than ferrous sulfate[29]	Often sold in liquid form; better absorbed than ferrous sulfate tablets. A higher dosage may be needed because this form contains less elemental iron[29]
Ferrous fumarate	33% elemental iron per mg ferrous fumarate salt[27]	Similar in efficacy to ferrous sulfate and ferrous gluconate[27]	Adverse effects similar to those of ferrous sulfate and ferrous gluconate[27]
Iron protein succinylate	Ferric iron bound to protein; separates into elemental iron in intestines instead of in stomach[33]	More expensive than iron salts[27]	May cause fewer GI adverse effects (metallic taste) than iron salts.[27] Has lowest rate of adverse effects and comparable efficacy to iron salts[33]
Ferrous bisglycinate		More expensive than iron salts[32]	May cause fewer GI adverse effects

GI: gastrointestinal

Iron replacement can be oral or IV. Oral replacement is effective, safe, inexpensive, easy to obtain, and easy to administer.[27] Oral replacement is recommended for adults whose anemia is not severe or who do not have a comorbid condition such as pregnancy, inflammatory bowel conditions, gastric surgery, or chronic kidney disease. When anemia is severe or a patient has one of these comorbid conditions, IV is the preferred method of replacement.[27] In these cases, defer treatment to the patient's primary care physician or specialist.

There are no clear recommendations on the amount of iron per dose to prescribe.[27] The maximum amount of oral iron that can be absorbed is approximately 25 mg/d of elemental iron. A 325 mg ferrous sulfate tablet contains 65 mg of elemental iron, of which approximately 25 mg is absorbed and utilized.[27]

Emerging evidence suggests that excessive iron dosing may reduce iron absorption and increase adverse effects. In a study of 54 nonanemic young women with iron deficiency who were given iron supplementation, Moretti et al[28] found that a large oral dose of iron taken in the morning increased hepcidin, which decreased the absorption of iron taken later for up to 48 hours. They found that 40 to 80 mg of elemental iron given on alternate days may maximize the fractional iron absorbed, increase dosage efficacy, reduce GI exposure to unabsorbed iron, and improve patients' ability to tolerate iron supplementation.[28]

Adverse effects from iron supplements occur in up to 70% of patients.[27] These can include metallic taste, nausea, vomiting, flatulence, diarrhea, epigastric pain, constipation, and dark stools.[27] Using a liquid form may help reduce adverse effects because it can be more easily titrated.[27] Tell patients to avoid enteric-coated or sustained-release iron capsules because these are poorly absorbed. Be cautious when prescribing iron supplementation to older adults because these patients tend to have more adverse effects, especially constipation, as well as reduced absorption, and may ultimately need IV treatment. Iron should not be taken with food, calcium supplements, antacids, coffee, tea, or milk.[27]

The amount of iron present, cost, and adverse effects vary by supplement. The ***Table***[27,29-33] provides more information on available forms of iron. Many forms of iron supplementation are

available over-the-counter, and most are equally effective.[27] Advise patients to use iron products that have been tested by an independent company, such as ConsumerLab.com. Such companies evaluate products to see if they contain the amount of iron listed on the product's label; for contamination with lead, cadmium, or arsenic; and for the product's ability to break apart for absorption.[34]

Six to 8 weeks of treatment with oral iron supplementation may be necessary before anemia is fully resolved, and it may take up to 6 months for iron stores to be repleted.[27] If a patient cannot tolerate an iron supplement, reducing the dose or taking it with meals may help prevent adverse effects, but also will reduce absorption. Auerbach[27] recommends assessing tolerability and rechecking the patient's CBC 2 weeks after starting oral iron replacement, while also checking hemoglobin and the reticulocyte count to see if the patient is responding to treatment. An analysis of 5 studies found that a hemoglobin measurement on Day 14 that shows an increase ≥1.0 g/dL from baseline predicts longer-term and sustained treatment response to continued oral therapy.[35] There is no clear consensus for target ferritin levels, but we suggest aiming for a ferritin level >100 ug/L based on recommendations for the treatment of restless legs syndrome.[36] We recommend ongoing monitoring every 4 to 6 weeks.

Related Resources

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Clinical Point

Advise patients to use an iron supplement that has been tested by an independent company

Bottom Line

Iron deficiency is common and can cause or contribute to psychiatric symptoms and disorders. Consider screening patients for iron deficiency and treating it with oral supplementation in individuals without any comorbidities, or referring them to their primary care physician or specialist.

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Iron deficiency

Clinical Point

We suggest aiming for a serum ferritin level >100 ug/L and monitoring every 4 to 6 weeks

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